INVESTIGATOR'S BROCHURE

ODRONEXTAMAB (REGN1979)

Sponsor: Regeneron Pharmaceuticals, Inc.
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Edition No.: 9
Date: *See appended electronic signature page*
Supersedes: Edition 8 dated 04 Mar 2022

The data cutoff date for this edition of the Investigator's Brochure is 18 September 2022 unless otherwise specified.

CONFIDENTIALITY STATEMENT

This page is signed by the investigator and retained in the Trial Master File.

INVESTIGATOR'S BROCHURE CONFIRMATION OF RECEIPT

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☐ That I am familiar with the appropriate use of the investigational product(s), as described in this Investigator's Brochure; and

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
BCL-2	B cell lymphoma 2
BCL-6	B cell lymphoma 6
B-NHL	B cell non-Hodgkin lymphoma
BR	Bendamustine and rituximab product
bsAb	Bispecific antibody
BTK	Bruton's tyrosine kinase
CAR-T	Chimeric antigen receptor T cell
C_{max}	Maximum (peak) concentration
C_{trough}	Trough concentration
CDC	Complement dependent cytotoxicity
CHO	Chinese hamster ovary
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
CVP	Cyclophosphamide, vincristine, prednisone
DL	Dose level
DLBCL	Diffuse large B cell lymphoma

Abbreviation	Definition
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GALT	Gut-associated lymphoid tissue
GLP	Good laboratory practice
HD-ASCT	High dose therapy with autologous stem cell transplantation
ICANS	Immune effector cell-associated neurotoxicity syndrome
IFN	Interferon
IL	Interleukin
IPI	International Prognostic Index
IRR	Infusion related reaction
IV	Intravenous
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MALT	Mucosa-associated lymphatic tissue
MedDRA	Medical Dictionary for Regulatory Activities
MCL	Mantle cell lymphoma
MIPI	MCL International Prognostic Index
MOA	Mechanism of action
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin Lymphoma
NK	Natural killer
NOAEL	No-observed-adverse-effect-level
NSG™	Non-obese diabetic SCID gamma
OECD	Organization for Economic Co-operation and Development
ORR	Objective response rate

Abbreviation	Definition
OS	Overall survival
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PT	Preferred term
QW	Once Weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
R2	Lenalidomide in combination with a rituximab product
R/R	Relapsed or refractory
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-CVP	Rituximab, cyclophosphamide, vincristine, prednisone
R-DHAP	Rituximab, dexamethasone, cytarabine (ara-C), cisplatin (platinum)
R-ICE	Rituximab, ifosfamide, carboplatin, etoposide
RBC	Red blood cell
RSI	Reference Safety Information
SAE	Serious adverse event
SAR	Serious adverse reaction
SCID	Severe combined immunodeficiency
SC	Subcutaneous
SCT	Stem cell transplant
SMQ	Standardized MedDRA query
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TCR	T cell receptor
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
US	United States

Abbreviation	Definition
WBC	White blood cell

SUMMARY OF CHANGES

Current Edition: Edition 9, 12 Feb 2023
Supersedes: Edition 8, 04 Mar 2022

Section Changed	Description of Change
1.1. Physical, Chemical, and Pharmaceutical Properties and Formulations	A sentence is added to describe how the drug product is supplied.
1.3 Clinical Summary	Summaries of the updated safety and efficacy profiles were added
5. Effect in Humans	This section is updated
5.1 Study Designs and Enrollment	The enrollment data is updated
5.2 Pharmacokinetics in Humans	This entire section is updated
5.3 Immunogenicity	This section header was added
5.4 Safety of Pooled Odronextamab Monotherapy Treatment Studies	The data for studies R1979-HM-1333 and R1979-ONC-1625 are updated in all subsections.
5.5 Safety of Combination Studies	There was no change to the data in this section; only editorial changes.
5.6 Efficacy	This section is updated for studies R1979-HM-1333 and R1979-ONC-1625
6. Guidance for the Investigators	This section is updated with updated data (including on modified regimen for odronextamab monotherapy) and important risk of infections updated to identified risk from potential risk. The list of expected serious adverse reactions (SARs) is updated to include infections (Table 37).
7. Overall risk and benefit	This section is updated to reflect the risk and benefit assessment based on the updated safety and efficacy data.

1. SUMMARY

1.1. Physical, Chemical, and Pharmaceutical Properties and Formulations

Odronextamab (REGN1979) is a human IgG4-based bispecific antibody (bsAb) that binds to CD3, a T cell antigen associated with the T cell receptor (TCR) complex, and CD20, a B cell surface antigen present on normal B cells and several B-cell lineage malignancies. Odronextamab is designed to bridge CD20-expressing cells with cytotoxic T cells by binding to the CD3 subunit of the TCR, resulting in CD20-directed polyclonal T cell killing. Odronextamab is a heterotetrameric protein containing two identical human kappa light chains, each covalently linked to 1 of 2 unique human gamma heavy chains; the 4 polypeptide chains are covalently combined in an IgG4 scaffold. The variable domains of the heavy and light chains combine to form the CD3 and CD20 binding sites within the bsAb.

REGN1979 drug product (DP) is supplied as a sterile liquid solution (3 concentrations- 2 mg/mL, 20 mg/mL and 100 mg/mL) in a glass vial for IV (2 mg/mL and 20 mg/mL) or subcutaneous (SC) (2mg/mL and 100mg/mL) administration.

1.2. NONCLINICAL SUMMARY

The nonclinical activity of odronextamab was evaluated in multiple in vitro assays, 2 different B cell lymphoma models using immuno-deficient mice transplanted with human immune cells (mouse-human chimera) and a single-dose pharmacology study in cynomolgus monkeys (Section 4.1).

The in vitro assays were performed to determine the ability of odronextamab to bind to various cells, and to activate and induce T cells to specifically kill CD20-expressing target cells. Odronextamab was shown to bind to both Raji cells, a CD20+ B cell lymphoma line, and Jurkat cells, an immortalized CD3+ T cell line, as well as to primary human B and T cells. Odronextamab induces the expression of T cell activation markers and induces T cell proliferation and cytokine release when cultured in the presence of CD20+ cells. In cellular cytotoxicity assays, odronextamab is able to target the killing of CD20-expressing cells in a specific manner. These in vitro assays were used to define a minimally active biologic equivalent level for odronextamab.

In vivo experiments utilizing mouse-human chimera tumor models were performed to evaluate the activity of odronextamab in a disease model. In the 2 mouse B cell lymphoma models, odronextamab targeted Raji (B cell) tumors, resulting in significant tumor growth suppression.

The pharmacokinetics (PK) and anti-tumor activity of odronextamab were evaluated in non-obese diabetic severe combined immunodeficiency (SCID) gamma (NSG™) immunodeficient mice bearing Raji tumors with single-dose intraperitoneal administration (dose level [DL] 0.04, 0.1, 0.4, or 1.0 mg/kg). Anti-tumor activity was seen at all odronextamab doses, with the higher doses of 0.4 and 1.0 mg/kg resulting in complete tumor suppression (Section 4.1).

A single dose, exploratory non-good laboratory practice (GLP) pharmacology study in male cynomolgus monkeys was conducted to examine the ability of odronextamab to deplete B cells in comparison to the standard of care anti-CD20 monoclonal antibody (mAb), rituximab. In this

study, odronextamab more effectively depleted B cells deep within lymphoid tissues of normal monkeys than rituximab.

The PK and toxicokinetic (TK) profiles of total odronextamab were evaluated in cynomolgus monkeys during a single-dose GLP PK study and single-and repeat-dose GLP toxicology studies. In general, the PK of total odronextamab in the monkey is described by non-linear, target-mediated elimination. Bioavailability of odronextamab following subcutaneous (SC) administration was approximately 82% (Section 4.2).

The toxicity profile of odronextamab was evaluated in an exploratory, non-GLP, single-dose intravenous (IV) infusion toxicology study (DL 1 mg/kg) and repeat-dose GLP-toxicology studies (DLs 0.01, 0.1, or 1 mg/kg). Tolerability following single-dose (up to 1 mg/kg) and step-up dose administrations (1/25/100 mg/kg) of odronextamab via IV infusion dosing and SC injection was also evaluated. Odronextamab resulted in B cell depletion at all doses tested, with earlier recovery at the lower doses. This depletion extended into deep tissues including lymph nodes and the spleen. A transient release of cytokines was observed whose magnitude correlated with the strength of the dose, and at the highest dose several animals also displayed some vomiting with the first dose. Neither cytokine release nor symptoms occurred upon second or subsequent dosing. Several animals were humanely euthanized in the repeat-dose toxicology studies due to deteriorating condition following consecutive days of liquid feces, dehydration, and/or low food consumption. Increased C-reactive protein (CRP) and neutrophil levels, and multiorgan inflammation, including the gastrointestinal tract, were observed in these animals. These findings are consistent with acute inflammation and are likely to be the result of an opportunistic infection due to sustained B cell depletion.

An ex vivo tissue cross-reactivity study was also conducted to assess the binding specificity of odronextamab in a panel of human and cynomolgus monkey tissues. All staining in this study was consistent with expected reactivity with the target antigens, and no unanticipated cross-reactivity of odronextamab was observed (Section 4.3.7).

1.3. CLINICAL SUMMARY

Odronextamab is currently being evaluated as monotherapy for the treatment of patients with CD20+ B cell malignancies previously treated with anti-CD20 antibody therapy in a Phase 1 study R1979-HM-1333 and a Phase 2 study R1979-ONC-1625 (Table 7). In addition, odronextamab in combination with cemiplimab is being evaluated for the treatment of patients with relapsed or refractory (R/R) B cell non-Hodgkin Lymphoma (B-NHL) in a Phase 1 study R1979-ONC-1504 (Table 7). One patient with acute lymphoblastic leukemia (ALL) received odronextamab monotherapy in study R1979-ONC-1504, and the evaluation of odronextamab monotherapy in patients with ALL has been closed.

The safety profile of odronextamab was assessed primarily from a pooled analysis of 539 patients who received monotherapy treatment in studies R1979-HM-1333, R1979-ONC-1625, and R1979-ONC-1504. Additionally, the safety profile of odronextamab in combination with cemiplimab was assessed for 32 patients in R1979-ONC-1504. As of the data cutoff date of 18 September 2022, a total of 571 patients received odronextamab with 539 patients receiving odronextamab monotherapy treatment with an estimated patient exposure of 15039 weeks. A total

of 32 patients received odronextamab in combination with cemiplimab treatment, with an estimated patient exposure of 449.7 weeks (Section 5.4.2).

Frequently reported treatment-related treatment-emergent adverse events (TEAEs, all grades) for odronextamab monotherapy were cytokine release syndrome (CRS) (n=301, 55.8%), pyrexia (n=195, 36.2%), infusion related reaction (IRR) (n=129, 23.9%), and anaemia (n=111, 20.6%) (Section 5.4.5). A total of 322 of 539 patients (59.7%) treated with odronextamab monotherapy experienced Grade ≥3 treatment-related TEAEs (assessed by the investigators). The most frequently reported Grade ≥3 treatment-related TEAEs were neutropenia (n=73, 13.5%) and anaemia (n=54, 10.0%).

A total of 235 of 539 patients (43.6%) experienced serious treatment-related TEAEs (Section 5.4.5.2). The most frequently reported serious treatment-related TEAE with odronextamab monotherapy was CRS (n=118, 21.9%).

Adverse events of special interest (AESI) for patients treated with odronextamab monotherapy are summarized in Section 5.4.6. These included CRS and IRRs, tumor lysis syndrome (TLS), neurotoxicity (immune effector cell-associated neurotoxicity syndrome [ICANS]), and infections.

Safety data for patients treated with odronextamab in combination with cemiplimab is presented in Section 5.5.

Efficacy data as of 18 Sep 2022 for patients with DLBCL (with or without prior CAR-T treatment) treated with odronextamab monotherapy at a full dose of 160 mg, and FL grade 1-3 treated at a full dose of 80 mg, are summarized in Section 5.6.

2. INTRODUCTION

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of malignancies with lymphoid characteristics that arise from hematopoietic progenitor cells. Collectively, NHLs comprise the seventh most common malignancy and account for approximately 4.5% of all cancers occurring in the United States (US). In the US, there was approximately 80,470 new cases and 20,250 deaths due to NHL in 2022 (American Cancer Society, 2022). In Europe, the estimated incidence of NHL was 122,979 in 2020 with a mortality of 49,684 (Global Cancer Observatory, 2020).

The largest proportion of NHLs (>90%) are of B cell origin, and the remainder are T/natural killer (NK)-cell lymphomas or are of indeterminate or mixed lineage (Teras, 2016). NHLs are commonly grouped into those that exhibit an initially indolent clinical course (such as follicular lymphoma [FL]) and those that are typically aggressive (such as diffuse large B cell lymphoma [DLBCL]).

B cell NHLs have the molecular and cell surface characteristics of normal B cell differentiation, and those with greater lineage maturation express the CD20 marker. CD20 is typically highly expressed (as measured by "bright staining" using immunohistochemistry) in FL and is of weaker intensity in small lymphocytic lymphoma (Craig et al, 2008). Overall, CD20 expression is prevalent but is variable both between and within different lymphoma subtypes (Olejniczak, 2006).

2.1. Follicular Lymphoma

Follicular lymphoma is the most common indolent lymphoma in the US and Western Europe, accounting for approximately 70% of all indolent NHLs and 25% of all B-NHLs (Swerdlow, 2017) (Teras, 2016), and a median survival of 8 to 10 years. The prognosis in patients with FL is dependent on identified clinical risk factors (eg, Follicular Lymphoma International Prognostic Index [FLIPI] score). Patients with advanced FL generally are not cured with available conventional therapies, and the relapse rate remains consistent over time despite achievement of response during the initial disease course. Transformation to an aggressive lymphoma occurs at a rate of 12.8% and 19.4% at 5 and 8 years, respectively (Wagner, 2015).

In patients with FL without significant comorbidities, the combination of anti-CD20 antibody (obinutuzumab or rituximab) with chemotherapy (eg, bendamustine, CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone], or CVP [cyclophosphamide, vincristine, prednisone] is considered standard of care in first-line treatment. For patients who are elderly and considered unfit for the above regimens, treatment options include rituximab alone, chlorambucil or cyclophosphamide with or without rituximab, or ibritumomab tiuxetan. Patients who progress after 1 line of therapy may consider other standard regimens used in frontline treatment based on their performance status. Despite the presence of multiple treatment options, FL remains an incurable disease, and patients typically relapse, requiring successive therapeutic options. Lenalidomide (Revlimid®) in combination with rituximab is approved in the US and European Union (EU) for the treatment of adult patients with previously treated FL (REVLIMID® USPI, 2019). Lenalidomide with rituximab yielded a median progression-free survival (PFS) of 39 months in a Phase 3 study of 358 patients (82% had FL; median 1 prior treatment), compared to 14 months with rituximab alone (Leonard, 2019). Of note, patients with rituximab-refractory disease were excluded in this study.

In the third line setting, rituximab-based chemo-immunotherapy regimens or phosphoinositide 3-kinase (PI3K) inhibitors, including idelalisib, copanlisib, and duvelisib, may be used. Idelalisib was the first PI3K (delta isoform) inhibitor that received accelerated approval in the US in 2014 in this setting. However, in 2016, 6 clinical trials using idelalisib in combination with other cancer drugs were stopped due to high rates of serious adverse events (SAE), including multiple deaths (ZYDELIG® USPI, 2018) (COPIKTRA® USPI, 2020).

Copanlisib, a PI3K alpha/delta isoform inhibitor, received accelerated approval in the US in 2017, based on a Phase 2 study (CHRONOS-1) for patients who had relapsed or were refractory to ≥2 prior lines of treatment and previously treated with rituximab and an alkylating agent. In the CHRONOS-1 study, the ORR was 59.2%, including a CR rate of 12% and a PR rate of 47.2%, along with an observed median DOR of approximately 370 days (Deyling, 2017).

Duvelisib, a PI3K-δ/γ isoform inhibitor, received accelerated approval in the US in 2018, and in the EU in 2021 based on a Phase 2 study (DYNAMO), which enrolled 83 patients with FL whose disease was refractory to rituximab (Rituxan®) and either chemotherapy or radioimmunotherapy (COPIKTRA USPI 2020). The ORR was 42%, a CR rate of 1% and PR rate of 41% (Flinn, 2019).

Tazemetostat, an EZH2 inhibitor, received accelerated approval by the Food and Drug Administration (FDA) in 2020 based on 2 single-arm cohorts (EZH2-mutated FL and EZH2 wild-type FL) for adult patients with R/R FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for patients with R/R FL who have no satisfactory alternative treatment options. EZH2-mutated FL cohort had an ORR of 69% and CR rate of 12%, and the EZH2 wild-type FL cohort had an ORR of 34% and CR rate of 4% (TAZVERIK® USPI, 2020).

Axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor T cell (CAR-T) therapy, received approval by FDA in 2021 based on a single-arm, open-label, study (ZUMA-5) in adult patients with refractory or relapsed FL after ≥2 lines of systemic therapy, including the combination of an alkylating agent and an anti-CD20 mAb. The ORR in the study was 91% and the CR rate was 60% (YESCARTA® USPI, 2022).

In summary, while patients with R/R FL have few treatment options at present, response rates and durability of response are limited, and there continues to be a need for therapies which can improve upon current standards.

2.2. Diffuse Large B Cell Lymphoma

Diffuse large B cell lymphoma is the most common subtype of NHL and accounts for approximately one-third of all newly diagnosed cases. Similar to FL, clinical risk factors have been identified to assess prognosis in patients with aggressive NHL, using the International Prognostic Index (IPI) for aggressive NHL. Patients with ≥2 risk factors have a less than 50% chance of relapse-free survival and overall survival (OS) at 5 years. Additionally, molecular markers have been identified that are known to confer a poor prognosis, in particular MYC, B cell lymphoma 2 (BCL-2), and B cell lymphoma-6 (BCL-6) rearrangements, as well as molecular prognostic characteristics defined by gene expression profiling(Schmitz, 2018).

For patients with newly diagnosed aggressive B cell lymphoma such as DLBCL, chemoimmunotherapy with anti-CD20 antibody and an anthracycline-based regimen (often

R-CHOP) is the standard. Approximately 50% of patients will respond and continue to be in remission at 5 years. For those patients who either relapse or have refractory disease, there is no standard salvage regimen. Patients are often treated with chemotherapy regimens (including R-ICE [rituximab, ifosfamide, carboplatin, etoposide phosphate] or R-DHAP [rituximab, dexamethasone, cytarabine, cisplatin) with the plan to proceed to high dose therapy with autologous stem cell transplantation (HD-ASCT) if the disease proves to be chemotherapy sensitive and the patient can tolerate the aggressive treatment. Patients who have chemotherapy-insensitive disease (approximately 35%) and/or are ineligible for HD-ASCT (approximately 50%) have a particularly poor prognosis, and in some studies these patients demonstrated a median OS of only 4 months (Friedberg, 2011). In addition, 2 anti-CD19 CAR-T therapies, axicabtagene ciloleucel and tisagenlecleucel, received marketing approvals to treat adult patients with R/R DLBCL after ≥2 lines of systemic therapy. The assessment of duration of the response and OS benefit is evolving and is not at this time well understood.

The outcomes for patients who do not respond to CAR-T therapy or those who have PR are poor. The median OS in patients with progressive disease at initial evaluation after CAR-T therapy was 5.1 months and 13.6 months in patients with a delayed progression of their disease (Chow, 2018). Moreover, there was no difference in survival for these patients if a second CAR-T infusion is administered compared to that when another therapy is provided. There are no therapies of proven benefit for patients who progress following CAR-T therapy, and thus there is a high need for novel salvage therapies after CAR-T failure.

In 2019, polatuzumab vedotin, an anti-CD79b antibody drug conjugate, received accelerated approval by the FDA, indicated in combination with bendamustine and a rituximab product (BR) for adult patients with R/R DLBCL after at least 2 prior lines of therapy based on a randomized study. In the polatuzumab vedotin plus BR arm, ORR was 45% and CR rate was 40%; in the BR arm, ORR was 18% and CR rate was 18% at the end of treatment. The DOR at 12 months was 48% in the polatuzumab vedotin plus BR arm and 20% in the BR arm (POLIVY® USPI, 2019).

Tafasitamab, a CD19-directed cytolytic antibody, received accelerated approval by FDA in 2020, and conditional approval in the EU in 2021, indicated in combination with lenalidomide for adult patients with R/R DLBCL who are not eligible for ASCT. Efficacy showed best ORR of 55%, CR rate of 37%, and median DOR of 21.7 months (MONJUVI® USPI, 2020).

Selenexor, a selective inhibitor of nuclear export, was granted accelerated approval by FDA for adult patients with R/R DLBCL, not otherwise specified, including DLBCL arising from FL, after at least 2 lines of systemic therapy. The ORR was 29% and the CR rate was 13%. Among the responders, 38% had DOR of at least 6 months and 15% had DOR of at least 12 months (XPOVIO® USPI, 2019).

Lisocabtagene maraleucel, a CD19-directed genetically modified autologous T cell immunotherapy, was approved by FDA in 2021 for the treatment of adult patients with R/R large B cell lymphoma (including DLBCL not otherwise specified [including DLBCL arising from indolent lymphoma], high-grade B cell lymphoma, mediastinal large B cell lymphoma, and FL Grade 3) after ≥2 lines of systemic therapy. In the TRANSCEND single-arm, open-label study, the ORR was 73% with a CR rate of 54%, and a median DOR or 16.7 months (BREYANZI® USPI, 2021).

Loncastuximab, a CD19-directed antibody and alkylating agent conjugate, was granted accelerated approval by FDA in 2021 for adult patients with R/R large B cell lymphoma (including DLBCL not otherwise specified, arising from low grade lymphoma, and arising from high grade B cell lymphoma) after ≥2 lines of systemic therapy, based on a single-arm, open-label study (LOTIS-2). The ORR was 48.3%, with a CR rate of 24.1%, and a median DOR of 10.3 months (ZYNLONTA® USPI, 2021).

In summary, while patients with R/R DLBCL have few treatment options at present, response rates and durability of response are limited, and there continues to be a need for therapies which can improve upon current standards.

2.3. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma is a mature B cell neoplasm characterized by clonal proliferation of B lymphocytes. In frontline treatment, the combination of rituximab with fludarabine and cyclophosphamide is considered standard of care. Other standard therapies include bendamustine with anti-CD20 antibody, or ibrutinib (Bruton's tyrosine kinase [BTK] inhibitor). For patients who have relapsed or have refractory disease, options include ibrutinib, acalabrutinib (BTK inhibitor), venetoclax (BCL-2 inhibitor), or idelalisib with or without rituximab. Allogeneic stem cell transplantation (SCT) may be considered in patients with high-risk features such as del(17p) or TP53 mutation after failure of ibrutinib and often after venetoclax therapy. There is an unmet medical need for patients with CLL who have R/R disease and those who are elderly or frail and cannot tolerate chemotherapy.

Given the limitations of current anti-CD20 treatments and the remaining medical need for effective treatments for both NHL and CLL, Regeneron has developed the bispecific mAb, odronextamab to treat CD20+ B cell lymphomas. The mechanism of action (MOA) of odronextamab is distinct from those that are believed to underlie currently available CD20 directed therapies and may thus provide additional therapeutic benefit.

2.4. Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) comprises approximately 7% of B-NHL in the US and Europe. It is characterized in the majority of cases by a t (11;14) chromosomal translocation that results in dysregulation of cyclin D1 gene (*CCND1*) expression. The majority of patients have aggressive course at the time of initial diagnosis and are treated with chemoimmunotherapy consisting of BR or R-CHOP as initial therapy. The addition of rituximab to CHOP was shown to provide an ORR of 94% and CR rate of 34% (Lenz, 2005). The MCL International Prognostic Index (MIPI) is used as a prognostic stratification tool for patients with MCL. In a recent report, 5-year OS rates in MIPI low, intermediate, and high-risk groups were 83%, 63%, and 34%, respectively (Hoster, 2014).

Three BTK inhibitors, ibrutinib, acalabrutinib, and zanubrutinib have received accelerated approval from the US FDA for previously treated patients with MCL based on single arm studies. Ibrutinib and acalabrutinib are approved in the EU for the MCL indication (IMBRUVICA SMPC, 2022) (CALQUENCE SMPC, 2020). In an open-label study of ibrutinib in previously treated patients with MCL, an ORR of 65.8% and CR rate of 17.1% was observed with a median DOR of 17.8 months (IMBRUVICA® USPI, 2019). In the Phase 2 study of acalabrutinib (Trial LY-004) in patients with MCL who received at least 1 prior line of therapy, an ORR of 80% and CR rate of

40% was noted (CALQUENCE® USPI, 2017). In the single-arm Phase 2 study of zanubrutinib in 86 patients with MCL who received at least 1 prior therapy, the ORR was 84%, the CR rate was 59%, and the median DOR was 19.5 months (BRUKINSA® USPI, 2019).

Despite encouraging overall response rates, patients have a very poor prognosis after ibrutinib failure. The median OS of patients after cessation of ibrutinib has been reported to be only 2.9 months (Martin, 2016). The median OS of patients not receiving post-ibrutinib treatment and those receiving subsequent therapy after ibrutinib failure was 0.8 months and 5.8 months respectively. There are no proven therapies that have shown benefit after ibrutinib failure, and there is an important need for therapies in R/R MCL.

Brexucabtagene autoleucel (TECARTUS®), a CD19-directed CAR-T therapy received accelerated approval from the US FDA and conditional approval in EU for the treatment of adult patients with R/R MCL based on single-arm trial of 74 patients with R/R MCL. Of all 74 leukapheresed patients, the ORR was 80% with a CR rate of 55%. The estimated median DOR was not reached (range of 0+ to 29.2+ months) after a median follow-up time for DOR of 8.6 months (TECARTUS® USPI, 2020).

In summary, while patients with R/R MCL have few treatment options at present, response rates and durability of response are limited, and there continues to be a need for therapies which can improve upon current standards.

2.5. Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) originates from memory B lymphocytes in the marginal zone of lymphoid follicles of the spleen, mucosal-associated lymphoid tissues, and lymph nodes. Marginal zone lymphoma accounts for 8%–12% of all B-NHLs. Based on the site of involvement and molecular characteristics, MZL is classified into 3 subtypes comprising extranodal MZL, also called mucosa-associated lymphatic tissue (MALT) lymphoma, splenic MZL, and nodal MZL. The initial therapy for MZL differs greatly based upon the subtype and underlying etiology. Marginal zone lymphoma that is associated with a viral or bacterial etiology is treated with antiviral or antibacterial therapy as primary treatment. However, patients with advanced disease are often treated with chemoimmunotherapy, similar to that for other indolent lymphomas. In a prospective, randomized trial of BR versus R-CHOP as first-line treatment in indolent lymphomas, the median PFS was significantly greater in the BR group than in the R-CHOP group (Rummel, 2013). In a single arm, Phase 2 study of BR in MALT lymphoma, event-free survival at 2 years and 4 years was 93% and 88% respectively (Salar, 2014).

Treatment for relapsed or treatment-refractory MZL is similar to that of other indolent B-NHL subtypes such FL. Various chemoimmunotherapy regimens have been used in R/R MZL (Deyling, 2013). In the Phase 2 CHRONOS-1 study, copanlisib monotherapy in patients with R/R MZL (n=23) demonstrated an ORR of 70% and CR rate of 9% (Deyling, 2017b). Ibrutinib received accelerated approval by US FDA in 2017 for treatment of R/R MZL in patients who had at least 1 prior line of therapy based on a single arm Phase 2 trial, which demonstrated an ORR of 48% and a CR rate of 3%. At a median follow-up of 19.4 months, the median PFS was 14.2 months, and the median OR was not yet reached (IMBRUVICA® USPI, 20[1]9). However, the low CR rate and treatment failures present an unmet need for curative therapies in R/R MZL. In 2019, US FDA approved lenalidomide in combination with a rituximab product (R2) for previously treated MZL.

For patients with MZL in the AUGMENT study, the ORR was 65% in the R2 arm compared to 44% in the control arm. In the MAGNIFY study, the ORR was 59% for patients with MZL treated with R2 and the median DOR was not reached, with a median follow-up time of 7.9 months (REVLIMID® USPI, 2019).

In summary, while patients with R/R MZL have few treatment options at present, response rates and durability of response are limited, and there continues to be a need for therapies which can improve upon current standards.

3. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

3.1. Description of Molecule

Odronextamab is a human IgG4-based bsAb that binds to CD3, a T cell antigen associated with the TCR complex, and CD20, a B cell surface antigen present on normal B cells and several B cell lineage malignancies. Odronextamab is a heterotetrameric protein containing 2 identical human kappa light chains, each covalently linked to 1 of 2 unique human gamma heavy chains; the 4 polypeptide chains are covalently combined in an IgG4 scaffold through disulfide bonds. The 2 heavy chain polypeptides (HC and HC*) possess complementarity-determining regions involved in the binding of odronextamab to human CD20 and CD3, respectively. The antibody possesses a molecular weight of 145.6 kDa, calculated based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region of the Fc domain.

Antibody generation by VelocImmune® mice is carried out using standard techniques after immunization with CD20 and CD3. The genes encoding the heavy and light chains of odronextamab were introduced into Chinese hamster ovary (CHO) cells, and a stable expression cell line (cell line 1) was selected for the antibody. Later in development, a second stable expression cell line with a higher titer (cell line 2) was developed for this antibody. For both cell lines, the recombinant CHO cells were grown in suspension culture where the recombinant antibody was expressed and secreted into the cell culture medium. Antibody is harvested via filtration and purified through a series of preparative column chromatographic and filtration steps.

3.2. Drug Product

3.2.1. Description for Intravenous and Subcutaneous Formulation

3.2.1.1. Formulations

Odronextamab drug product (DP) is formulated in an aqueous buffered solution at pH 5.8 containing 10 mM histidine, 0.1% (w/v) polysorbate 80, and 10% (w/v) sucrose. All odronextamab DP are supplied as a sterile liquid solution in glass vials. Three concentrations of odronextamab DP are available: 2 mg/mL with nitrogen overlay, 20 mg/mL, and 100 mg/mL.

The 2 mg/mL and 20 mg/mL DPs are used for IV administration, while 2 mg/mL, 100 mg/mL DPs are used for SC administration, as shown below:

- DPs available for IV administration: 2 mg/mL, 20 mg/mL
- DPs available for SC administration: 2 mg/mL, 100 mg/mL.

3.2.2. Storage and Stability

Study drug is stored at the study sites at 2°C to 8°C. The temperature of the storage refrigerator at each study site should be checked and recorded at least daily.

Based on ongoing long-term, accelerated, and stress stability studies, the product/study drug is stable for use in the clinical development program for odronextamab.

Details on storage and preparation for DP for IV or SC administration are provided in the pharmacy reference manual.

4. NONCLINICAL STUDIES

4.1. Nonclinical Pharmacology

Odronextamab binds both CD20 and CD3 on human and cynomolgus B and T cells. Through this binding, odronextamab activates T cell populations of human and cynomolgus origin and directs those T cells to specifically kill CD20-expressing target cells.

The primary MOA of odronextamab is through directed T cell-mediated killing of CD20+ target cells, because odronextamab-bound Fcγ receptors with no or low affinity did not induce antibody-dependent cellular cytotoxicity (ADCC), and only showed weak complement dependent cytotoxicity (CDC) activity. Odronextamab induced CDC activity with far lower potency than that of the positive control antibody, and thus CDC is not expected to be a mode of action.

In 2 mouse B cell lymphoma models, odronextamab targeted Raji (B cell) tumors, resulting in significant tumor growth suppression. Also, in a single-dose monkey pharmacology study with rituximab and odronextamab administered as monotherapy, odronextamab more effectively depleted B cells deep within lymphoid tissues of normal monkeys than rituximab.

Odronextamab was evaluated in combination with cemiplimab both in vitro and in vivo. In whole blood and plate-bound assays, odronextamab in combination with cemiplimab did not further increase the level of cytokine production or induction of the activation marker CD69 on T cells when compared to either odronextamab alone or in combination with an isotype control antibody. An in vitro study of odronextamab in combination with a surrogate anti-mouse PD-1 antibody in immunocompetent mice humanized for CD20 and CD3 ($CD20^{hum/hum}CD3^{hum/hum}$ mice) with mouse melanoma tumors expressing human CD20 (B16F10.9_hCD20) was conducted. In this study, treatment with odronextamab and the anti-PD-1 antibody showed significant inhibition of hCD20-expressing melanoma tumor growth compared to the control groups (vehicle control and isotype control antibody).

A summary of in vitro and in vivo studies characterizing the activity of odronextamab is presented in Table 1.

Table 1: Pharmacology Studies

Study Title [Study Number]	Objectives	Test System	Key Results
Determination of the Equilibrium Binding Constant for the Interaction of odronextamab with Human and Cynomolgus Fcγ Receptor Proteins [REGN1979-MX-14009]	To determine the kinetic binding parameters for the interaction of odronextamab with the family of Fcγ receptors from human and cynomolgus monkey.	Surface Plasmon Resonance (Biacore), recombinant human and cynomolgus monkey FcγRI and FcγRII/III receptor proteins were immobilized on the chip surface by anti-penta-histidine capture and odronextamab injected over the FcγRI and FcγRII/III captured surfaces.	Odronextamab did not bind to the high affinity FcγRI from human or cynomolgus monkey. Odronextamab binding to human FcγRIIa variants (H167 and R167) and monkey FcγRIIa were approximately 1.5- to 3-fold weaker relative to the control antibody. Odronextamab bound to low-affinity human and monkey FcγRIIb approximately 20- and 3-fold weaker, respectively, than those of the control antibody. Odronextamab showed detectable binding to FcγRIIIa (V176 variant); however, the affinity was too weak to be accurately determined ($K_D \geq 160\mu M$). Odronextamab was not observed to bind human FcγRIIIa (F176 variant) or human FcγRIIIb. The affinity for odronextamab binding to cynomolgus monkey FcγRIIIa protein was ~20-fold lower compared to that of the positive control antibody.
In Vitro Characterization of REGN1979 Binding to Cells from Human and Cynomolgus Monkey [REGN1979-MX-14010]	To evaluate odronextamab binding to human and cynomolgus monkey cells. To determine binding affinities and estimate CD3 receptor occupancy at the anticipated starting dose in humans.	Flow cytometric analysis was utilized to characterize the binding of odronextamab to Raji cells and Jurkat cells as well as primary human and cynomolgus B cells and primary human T cells.	Summary of Kinetic Binding Parameters for the Interaction of odronextamab with Jurkat and Raji Cells at 37°C Cell Type / k_{on} (M-1s-1) / k_{off} (s-1) / K_D (nM) Jurkat (CD3+) / $1.3x10^4$ / $8.0x10^{-5}$ / 6.2 Raji (CD20+) / $1.25x10^4$ / $1.28x10^{-3}$ / 102 Note: Similar K_D values (within less than 2-fold) were obtained for odronextamab incubated with either Jurkat cells at 4°C or odronextamab incubated with azide-treated Jurkat cells at 37°C Odronextamab bound human B cells with an EC_{50} of 57.9nM and bound human T cells with an EC_{50} of 37.7nM which is

Study Title [Study Number]	Objectives	Test System	Key Results
			comparable to the binding affinities observed in the Jurkat and Raji cell lines.
In Vitro Characterization of REGN1979 Activity [REGN1979-MX-14011]	To evaluate the ability of odronextamab to induce proliferation of human and cynomolgus PBMC.	Human or monkey PBMCs were incubated with odronextamab and a fixed concentration of an anti-CD28 antibody and the number of viable cells determined with a luminescence assay.	Odronextamab induced human or cynomolgus monkey PBMC proliferation with similar potency in the presence of a co-stimulatory anti-CD28 antibody. The odronextamab EC_{50} values (defined as the concentration of antibody required to generate half-maximal proliferation) were 54.9 pM for human PBMCs, and 33.3 pM for cynomolgus PBMCs. The IgG1 control antibody exhibited no activity in this assay.
	To evaluate the ability of odronextamab to activate T cells in human and cynomolgus whole blood.	Freshly isolated human or cynomolgus whole blood was incubated with odronextamab. To measure CD69 upregulation on T cells, a phenotyping cocktail containing directly conjugated antibodies to CD45, CD2, CD4, CD8, CD69 and either CD19 (human) or CD16 (cynomolgus) was added directly to the blood. RBCs were lysed and samples analysed by flow cytometry. Cytokine levels (TNFα, IFNγ, IL-6, IL-1β) in the human blood samples were analyzed using an electrochemiluminescent bridging assay. IFNγ and TNFα levels in the cynomolgus blood samples were analyzed by an ELISA method.	All 10 donors were tested for CD69 upregulation, and 9/10 donors were tested for REGN1979-induced cytokine release (IL-1β, IL-6, and TNFα [all 10 donors were tested for IFNγ release]). Odronextamab induced variable levels of proinflammatory cytokine release and upregulation of CD69 expression by human CD4+ T cells. A representative donor, odronextamab induced release of IFNγ and TNFα with EC_{50} values of 557 pM and 447 pM, respectively, and upregulated CD69 expression with an EC_{50} value of 57.7 pM.

Study Title [Study Number]	Objectives	Test System	Key Results
	To model the effect of anti-drug antibodies on cytokine release by cross-linking odronextamab on the surface of T cells.	Odronextamab was mixed with REGN654, an anti-human IgG constant region antibody. Freshly isolated human whole blood was added. After 20-hour incubation, plasma was removed and cytokine levels in the human samples were analyzed with an electrochemiluminescence bridging assay.	The addition of anti-hIgG slightly increased IFNγ production in whole blood (single donor) stimulated with 50 pM or 300 pM odronextamab; similar increases were seen for TNFα and IL-6. An increase in cytokine production was not seen in blood from a second donor. IL-1β was below the limit of quantification for both donors. The increase observed in the first donor did not result in levels of cytokine production that were outside of the normal range seen across donors
	To evaluate the ability of odronextamab to direct human or cynomolgus T cell mediated lysis of CD20-expressing Raji cells.	Human or cynomolgus PBMCs were isolated, activated with recombinant human IL-2 and T cell activation beads. CD20- expressing Raji cells were labeled with Calcein-AM and combined with the activated PBMCs and odronextamab. Cytotoxicity was measured with a fluorescence assay.	Odronextamab mediated target cell killing with representative EC_{50} values of 25.0 pM and 9.10 pM for human and cynomolgus T cells, respectively.
	To evaluate the ability of odronextamab to direct human or cynomolgus T cell mediated specific lysis of human CD20-expressing B16F10.9 cells (but not parental non-CD20 expressing B16F10.9 cells).	CD20-bearing B16F10.9 parental target cells (that do not express CD20) and CD20-expressing B16F10.9 cells were labeled with the fluorescent tracking dyes carboxyfluorescein diacetate succinimidyl ester (CFDA-SE) and Violet Cell Tracker, respectively. After labelling, cells were mixed at a 1:1 ratio, co-incubated with adherent cell-depleted naïve PBMC and odronextamab, and analyzed by FACS after staining with a dead/live far red cell tracker.	Odronextamab specifically directed human T cells to kill only target cells expressing CD20 in a mixed population of cells, as evidenced by a specific, dose dependent depletion of B16F10.9/CD20 cells. The observed target T cell lysis was associated with the presence of a CD69+ cell population. B16F10.9/CD20 cells were depleted up to 95%, with a representative EC_{50} value of 19.5 pM.

Study Title [Study Number]	**Objectives**	**Test System**	**Key Results**
Bioassay Determination of REGN1979 Potency [REGN1979-MX-14012]	To quantify the selectivity and potency of odronextamab stimulating CD3 T cell signalling on Jurkat cells stably transduced with a NFAT response element-luciferase reporter [Jurkat/NFAT-Luc], in the presence or absence of Raji cells expressing CD20.	The ability of odronextamab to stimulate CD3 T cell signalling on Jurkat cells stably transduced with a NFAT response element-luciferase reporter [Jurkat/NFAT-Luc] was studied in vitro in the presence or absence of Raji cells expressing CD20.	In the presence of Raji cells, odronextamab activated Jurkat/NFAT-Luc signalling with an EC_{50} value of 82 pM (defined as the concentration of REGN1979 required to stimulate CD3 signalling activity to 50% of the maximum activity level). No signalling activity was observed in the absence of Raji cells. A control IgG4P anti-CD3 antibody) induced minimal (less than 2-fold) luciferase response in Jurkat/NFAT-Luc cells in either the presence or absence of Raji cells. Neither REGN2534 (IgG4P anti-human CD20) nor REGN2579 (negative control) stimulated Jurkat/NFAT-Luc cells in the presence or absence of Raji cells.
Evaluation of Fc Effector Functions for REGN1979 [REGN1979-MX-14013]	To assess, in cell-based in vitro assays, the potential of odronextamab to utilize CDC effector function activity as part of its MOA. To assess, in cell-based in vitro assays, the potential of odronextamab to utilize ADCC effector function activity as part of its MOA.	In vitro cell-based assays were developed for measurement of ADCC and CDC in both CD3+ (Jurkat) and CD20+ (Raji) target cells.	Odronextamab demonstrated no ADCC activity using 2 different cell lines, suggesting that odronextamab -induced CD20-directed polyclonal T cell-mediated killing results from bridging of CD20-expressing tumor cells with cytotoxic T cells. Weak CDC activity of odronextamab was detected through the CD20 arm, but the activity was much less potent than the positive control anti-CD20 antibody.
In Vitro Characterization of Cytokine Accumulation in Whole Blood in Response to REGN1979 and cemiplimab [REGN1979-MX-15046]	To evaluate whether odronextamab in combination with cemiplimab produces an additive and/or synergistic effect on cytokine release.	Lymphocyte activation in whole blood was determined after 20 and 44 hours following stimulation by examining changes in the percentage of T cells expressing CD69 on the cell surface as well as by quantifying proinflammatory cytokine release. Concentrations of odronextamab, either alone or in combination with cemiplimab or isotype control, required to generate half maximal (EC_{50}) up-regulation	Odronextamab or odronextamab combined with cemiplimab resulted in similar levels of cytokine release (IFN-γ, IL-2, IL-6, IL-10 and TNFα) for multiple human donors and the frequency of T cells expressing CD69 increased to similar extents following treatment with odronextamab alone or in combination with cemiplimab.

Study Title [Study Number]	Objectives	Test System	Key Results
		of CD69 expression and cytokine production were determined.	
In Vitro Characterization of the T cell Response to Stimulation with Plate-bound REGN1979 and cemiplimab [REGN1979-MX-15100]	To analyse cytokine accumulation and T cell activation following culture of human PBMCs in an in vitro assay using immobilized antibodies.	REGN1979 was combined with either cemiplimab or an isotype control antibody and co immobilized onto assay plates in a similar manner and T cell activation and cytokine accumulation were measured.	Odronextamab co-captured onto plates with either cemiplimab or REGN1945 resulted in generally similar levels of cytokine release (IFN-γ, IL-2, IL-6, IL-10 and TNF-α) with PBMC from 3 different human donors. T cells from donors were examined for induction of the activation marker, CD69. The maximum frequency of T cells expressing CD69 across all donors was generally similar following stimulation with odronextamab in combination with cemiplimab or the isotype control.
Effect of REGN1979 on Raji Lymphoma Tumor Growth in Mice [REGN1979-MX-14014]	To evaluate the effects of REGN1979 on Raji tumor growth in hCD34+-engrafted SIRPα BRG mice.	Irradiated male and female immunodeficient SIRPα BRG pups were engrafted with human CD34+ hematopoietic stem cells, then implanted with Raji tumor cells at 3 months of age and treated immediately with REGN1979 or a hIgG1 non-binding control antibody.	Compared to the vehicle control and the non-binding control groups, odronextamab significantly suppressed Raji tumor outgrowth in a dose-dependent manner at doses of 0.04 mg/kg ($p<0.0001$) or 0.4 mg/kg ($p<0.0001$), as determined on Day 34 following tumor implantation.
	To evaluate the effects of REGN1979 on Raji tumor growth in NSG™ mice co-implanted with human PBMCs and Raji tumor cells.	Female NSG™ mice were engrafted SC with a mixture of human PBMCs and Raji tumor cells and treated with REGN1979 or a non-binding hIgG1 control antibody.	Compared to mice receiving the control antibody, twice-weekly dosing of odronextamab for 4 weeks completely suppressed Raji tumor outgrowth at doses of 0.004 mg/kg ($p<0.0001$), 0.04 mg/kg ($p<0.0001$) or 0.4 mg/kg ($p<0.0001$), as determined on Day 23 post tumor implantation.
Anti-Tumor Efficacy of REGN1979 [REGN1979-PH-17078]	To evaluate the PK and anti-tumor efficacy of REGN1979 in NSG™ mice bearing Raji tumors	Female NSG™ mice were implanted SC with a mixture of human PBMCs and Raji tumor cells and treated with single dose of REGN1979 or a vehicle control (PBS).	Anti-tumor activity was seen at all odronextamab doses tested, including 0.04, 0.1, 0.4 or 1.0 mg/kg. The higher doses of 0.4 and 1.0 mg/kg resulted in complete tumor suppression and showed similar terminal half-life of elimination (11 or 14 days), whereas lower doses of odronextamab (0.04 and 0.1 mg/kg) showed shorter terminal half-life (approximately 4 or 5 days) and resulted in tumor growth inhibition but not eradication.

Study Title [Study Number]	**Objectives**	**Test System**	**Key Results**
Anti-tumor Activity Study of REGN1979 in Combination with cemiplimab (Anti-PD-1) [REGN1979-MX-16073]	To evaluate REGN1979 in combination with a surrogate anti-mouse PD-1 antibody for anti-tumor activity against mouse melanoma tumors expressing human CD20 (B16F10.9_hCD20) in immunocompetent mice humanized for CD20 and CD3 ($CD20^{hum/hum}CD3^{hum/hum}$ mice).	$CD20^{hum/hum}CD3^{hum/hum}$ mice with established B16F10.9_hCD20 tumors were treated with REGN1979 (4 mg/kg twice per week for 3 weeks) in combination with a surrogate anti-mouse PD-1 antibody (10 mg/kg twice per week for 3 weeks).	There was significant inhibition of hCD20-expresssing melanoma tumor growth compared to the control groups (vehicle control and isotype control antibody). Similar results were observed in a second study using the same treatment regimen. No significant weight loss was observed in any treatment group in either study.
Single-Dose Monkey Pharmacology Study with Rituxan®, REGN1979, and REGN2280 Followed by a 1-Week Observation Period [REGN2280-TX-13140]	To evaluate the toxicity and determine the toxicokinetics of rituximab, and REGN1979 when given as a single dose via intravenous infusion to male cynomolgus monkeys and to assess any effects over at least 1 week of observation.	Male cynomolgus monkeys were given a single IV dose of REGN1979 (0.01, 0.1, or 1 mg/kg) or rituximab (30 mg/kg).	B cell values were, in general, quantitatively lower in lymphoid organs in animals given 0.1 or 1.0 mg/kg/dose of odronextamab than in animals given 30 mg/kg/dose rituximab.

ADCC, antibody- dependent cell- mediated cytotoxicity; BRG, Balb/c Rag2-/- γc-/-; CDC, complement dependent cell cytotoxicity; EC_{50}, Half maximal effective concentration; ELISA, enzyme-linked immunosorbent assay; FACS, fluorescence-activated cell sorting; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IV, Intravenous; K_D, equilibrium dissociation constant; k_{off}, off-rate constant; k_{on}, on-rate constant; MOA = mechanism of action; NFAT, nuclear factor of activated T cells; NSG™, Non-obese diabetic severe combined immunodeficiency gamma; PBMC, peripheral blood mononuclear cells; PBS, phosphate buffered saline; PK, pharmacokinetic(s); RBC, red blood cell; SIRP, signal-regulatory protein; TNF, tumor necrosis factor.Rituxan® (rituximab); REGN1979 (odronextamab).

4.1.1. Safety Pharmacology

Dedicated safety pharmacology studies were not conducted with odronextamab. Instead, safety pharmacology endpoints were integrated into the repeat-dose monkey toxicology studies with odronextamab given IV at doses up to 1 mg/kg once weekly (QW) over up to 16 weeks (Section 4.3.3). Safety pharmacology endpoints included an evaluation of cardiac conduction (electrocardiograms [ECG] and heart rate by jacketed external telemetry) and hemodynamics (blood pressure by tail cuff). During the in-life phase of the study, neurologic examinations were performed, and respiration rate was evaluated.

There were no odronextamab-related effects observed in cardiovascular, neurologic, or respiratory function in the evaluated species, nor were there any deleterious gross or microscopic changes observed in tissues associated with these systems.

4.2. Pharmacokinetics in Animals

The PK and TK profiles of total odronextamab were evaluated during a single-dose PK study in male cynomolgus monkeys and in single- and repeat-dose toxicology studies in male and female monkeys.

4.2.1. Single-Dose Pharmacokinetic Study

Twelve male cynomolgus monkeys (4/dose group for PK analysis) were given a single 30-minute IV infusion of odronextamab at doses of 0.001, 0.01, or 0.1 mg/kg. For immunophenotyping analysis, an additional four male monkeys (2/dose group) were given a single 30-minute IV infusion of odronextamab at doses of 0.001 or 0.01 mg/kg (REGN1979-PK-13085).

Blood samples were collected for measurement of total odronextamab concentrations in serum at pre-dose, and at pre-determined time points up to 9 or 10 weeks post-infusion. Blood samples were collected for immunophenotyping analysis (ie, B cell counts) twice at baseline (pre-study) and at pre-determined time points up to 10 weeks post-infusion. Anti-odronextamab antibodies (anti-drug antibodies [ADA]) were not determined by analytical methods; however, the individual concentration-time profiles were visually evaluated for any potential ADA impact.

Following a single IV infusion, mean total odronextamab serum maximum concentration (C_{max}) values in monkeys increased in an approximately dose-proportional manner. The concentration-time profile of total odronextamab was characterized by a short distribution phase, followed by a saturating beta elimination phase at higher doses and an accelerated target-mediated elimination phase at low doses (and corresponding low serum concentrations). Target-mediated elimination (presumably due to binding of odronextamab to the CD20 target on B cells) was observed in the distribution phase and correlated with the nearly complete depletion of B cells observed 24 hours post-infusion. The duration of peripheral B cell depletion increased with the odronextamab dose and in general, the rate of B cell repletion was positively correlated with the rate of clearance of total odronextamab.

4.2.2. Single-Dose Toxicokinetic Study

In a non-GLP exploratory toxicology study, 3 male cynomolgus monkeys were given a single 1 mg/kg dose of odronextamab by IV infusion followed by a 12-week observation period. A

control group received one IV infusion of sterile saline with 0.01% (w/v) polysorbate 80 (REGN2281-TX-13025).

Blood samples were collected for measurement of total odronextamab concentrations in serum at pre-dose and at pre-determined time points through Day 85. An anti-odronextamab antibody analysis was not performed in this study.

All drug-treated animals had detectable concentrations of total odronextamab from the first sampling time point (5 minutes post-infusion) through at least Day 67, indicating continuous exposure to total odronextamab throughout the majority of the study. Concentration-time profiles of total odronextamab were characterized by a short distribution phase followed by a prolonged elimination phase. A mean C_{max} value of 26.0 µg/mL was observed at the first sampling time point (5 minutes post-infusion) for the three animals. The apparent terminal half-life following the single dose was 14 days.

4.2.3. Repeat-Dose Toxicokinetic Studies

Systemic exposure to odronextamab was characterized in male and female cynomolgus monkeys during a 4-week, repeat dose, GLP toxicology study. Cynomolgus monkeys (6 animals/sex/group) were given 0.01, 0.1, or 1 mg/kg/week odronextamab by IV infusion for 4 weeks (total of 5 doses), followed by a 12-week recovery period. In addition, the PK/pharmacodynamic relationship between total odronextamab concentrations in serum and B cell counts in peripheral blood was determined (REGN1979-TX-13091).

Following 5 weekly IV infusions of odronextamab, the distribution phase was less apparent while the elimination phase was more prolonged, particularly at the higher doses which may have resulted in sustained depletion of circulating B cells. Mean total odronextamab serum C_{max} values increased in an approximately dose-proportional manner. The corresponding mean trough concentration (C_{trough}) values were approximately dose proportional after the first odronextamab dose and generally increased following successive infusions and then plateaued after the fifth infusion, indicating that steady-state had been achieved. With successive odronextamab doses, the approximate dose-proportionality of the C_{trough} values was only maintained in higher dose groups, suggesting that target-mediated elimination is more predominant at lower doses and concentrations. There were no gender differences observed in the serum TK profiles of total odronextamab. Based on visual inspection of the total odronextamab serum concentration-time profiles, ADA may also contribute to the expedited decrease in total odronextamab concentrations in a small number of animals.

Systemic exposure to odronextamab was also characterized in female cynomolgus monkeys in a study consisting of a single-dose phase (Phase 1) and an escalating-dose phase (Phase 2). Monkeys in the single-dose phase (4 to 6 animals/group) received a single SC dose of 0.1 or 1 mg/kg odronextamab, or a single IV dose of 1 mg/kg, while those in the subsequent escalating-dose phase (6 animals/group) received 3 escalating IV or SC doses of 1, 25, and 100 mg/kg odronextamab (1 dose every 4 days), followed by an 8-week recovery period (R1979-TX-18196).

Following a single IV infusion or SC injection of odronextamab, concentration-time profiles were characterized by an initial brief distribution (IV) or absorption (SC) phase followed by a single elimination phase during the treatment and recovery periods for the 0.1 mg/kg SC, and 1 mg/kg IV and SC dose groups. For cohorts administered 0.1 and 1 mg/kg SC, dose-proportional

increases in C_{max} were observed and dose-normalized exposure (AUC_{last}/Dose) were comparable across the 0.1 and 1 mg/kg SC dose groups, indicating dose-proportional increases in exposure. Following step-up dosing of IV infusion or SC injection of 1, 25, and 100 mg/kg odronextamab, concentration-time profiles were similar to those observed in the single-dose phase. Bioavailability for this SC dose group was estimated to be approximately 82%.

Lastly, systemic exposure to odronextamab was characterized in male and female cynomolgus monkeys during a 16-week, repeat-dose, GLP toxicology study. Monkeys (8 animals/sex/group) received 17 QW IV infusions of control article (6 animals/sex/group received vehicle), 0.1 or 1 mg/kg odronextamab, followed by a 14-week recovery period (R1979-TX-17190).

Following IV administration, continuous exposure to total odronextamab was maintained in 72% of animals (9 of 16 and 14 of 16 animals in the 0.1 and 1 mg/kg dose groups, respectively) throughout the 16-week treatment period, and detectable concentrations of total odronextamab were observed throughout the recovery period in 38% of animals (3 of 8 animals in both dose groups). Concentration-time profiles of total odronextamab are characterized by a brief distribution phase that is more prolonged after the initial dose and less pronounced after subsequent doses, followed by a single elimination phase throughout the treatment and recovery periods across both dose groups. Dose-normalized exposure (AUC_{tau}/Dose) values were comparable across both IV dose groups, indicating dose-proportional increases in exposure.

Accumulation of total odronextamab was observed following multiple dosing, as indicated by a 4.1- to 4.7-fold increase in mean C_{trough} from the first dose to the 17th dose across the 0.1 and 1 mg/kg dose groups. Steady-state concentrations of total odronextamab were achieved by approximately the eighth dose in both dose groups. The immunogenicity of odronextamab was dose-independent and low, with ADA-positive responses observed in 25% of drug-treated animals and an impact on exposure observed in 6% of animals.

4.3. Toxicology

The pivotal nonclinical toxicology studies related to odronextamab to support clinical development have been performed according to GLP in a country that is a signatory of the Organization for Economic Co-operation and Development (OECD) Mutual Acceptance of Data system in accordance with the OECD Test Guidelines and Principles of GLP.

The nonclinical safety studies conducted to support development of odronextamab are summarized in Table 2.

Table 2: Summary of the Odronextamab Toxicology Studies

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Dosing Frequency	Doses (mg/kg)	Gender and No. Per Group	Study Number/Title (Compliance)
Cynomolgus monkey (*Macaca fascicularis*)	IV infusion Vehicle: (1x DPBS, pH 7.2) Control Article: 0.9% sodium chloride	once	1	3 males/group	REGN2281-TX-13025[a]/ Exploratory Intravenous Infusion Toxicity and Toxicokinetic Study with REGN2280, REGN2281, REGN2147, REGN1979, and REGN1453 in Male Cynomolgus Monkeys Followed With a 12-Week Observation Period (non-GLP)
Cynomolgus monkey (*Macaca fascicularis)*	IV infusion (10 mM histidine, 10% [w/v] sucrose, 0.1% [w/v] polysorbate 80, pH 5.8)	once weekly for 4 weeks (total of 5 doses)	0, 0.01, 0.1, or 1	6 animals/ sex/group[b]	REGN1979-TX-13091/ REGN1979: 4-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 12-Week Recovery Period (GLP)
Cynomolgus monkey (*Macaca fascicularis)*	IV infusion	Once weekly for 16 weeks (total of 17 doses)	0, 0.1, or 1	6 animals/ sex/group for controls and 8 animals/ sex/group for the remaining groups	R1979-TX-17190/ REGN1979: A GLP 16-Week Repeat-Dose Intravenous Infusion Toxicity and Toxicokinetic Study with REGN1979 in Cynomolgus Monkeys Followed by at Least a 14-Week Recovery Phase (GLP)
Cynomolgus monkey (*Macaca fascicularis)*	IV infusion or SC injection	Single dose or repeat step-up doses once every 4 days for the repeat-dose phase	0, 0.1, or 1 (single dose phase); 1/25/100 in the step-up dose phase[c]	4 females for controls and 6 females in the repeat-dose escalation phase for odronextamab-treated groups	R1979-TX-18196/ REGN1979: A Single Dose Intravenous and Subcutaneous Toxicology and PK study in Cynomolgus Monkeys with up to an 8-Week Recovery Period (GLP)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Dosing Frequency	Doses (mg/kg)	Gender and No. Per Group	Study Number/Title (Compliance)
Normal human and cynomolgus monkey (*Macaca fascicularis)* tissues	NA	NA	2 and 10 µg/mL	NA	REGN1979-TX-13092/ A Tissue Cross-Reactivity Study of Biotinylated REGN1979 in Normal Human and Cynomolgus Monkey Tissues (GLP)

DPBS, Dulbecco's phosphate-buffered saline; GLP,Good Laboratory Practice; IV, Intravenous; NA, Not applicable; PK, pharmacokinetic(s); SC, subcutaneous.

[a] Study information presented here is only representative of Group 5 (animals given odronextamab).

[b] A subset of animals (3 animals/sex/group) were sacrificed at the end of the dosing period and the remaining animals (3 animals/sex/group) were maintained for 12 weeks.

[c] The second dose for animals administered IV or SC in the step-up phase at 25 mg/kg was given 4 days after the first dose of 1 mg/kg. The third dose of 100 mg/kg for these animals was administered 4 days after the second dose.

The key findings from these studies are summarized below, and details of each study are provided in the following sections.

- IV infusion of odronextamab QW was tolerated in the 4-week repeat-dose toxicology study in cynomolgus monkeys at DLs up to 1 mg/kg. Odronextamab-related depletion of B cells in the peripheral blood and decreased cellularity of several lymphoid tissues were observed at all DLs in all studies. There was a transient odronextamab-related increase in tumor necrosis factor (TNF)α, interleukin (IL)-2, IL-6, and interferon (IFN)-γ cytokines and decrease in peripheral T cells; these effects were not observed after any subsequent doses. There were no odronextamab-related effects on body temperature, blood pressure, respiration rate, blood oxygen saturation, heart rate, or neurological, ophthalmic, or ECG endpoints.
- Several animals were humanely euthanized in the 16-week study and during the recovery phase of the 4-week study due to rapid deterioration following consecutive days of liquid feces (positive for *Campylobacter*), dehydration and/or low food consumption. Increased CRP and neutrophils and multiorgan inflammation, including the gastrointestinal tract, were observed in these animals. These findings are consistent with acute inflammation and are likely the result of an opportunistic infection due to sustained B cell depletion.
- Subcutaneous injections of odronextamab administered as a single dose up to 1 mg/kg or step-up doses once every 4 days at 1 mg/25 mg/100 mg/kg were well tolerated at the injection site and resulted in lower cytokine release compared to IV infusion at the same DLs.
- An ex vivo tissue cross-reactivity study in human (adult and fetal) and cynomolgus monkey tissues showed the expected staining of mononuclear leukocytes based on the known expression of CD3 by T cells and CD20 by B cells, which are the target antigens for odronextamab.

4.3.1. Single Dose Toxicology Study in Cynomolgus Monkeys Following IV Infusion

A single dose, exploratory (non-GLP) IV infusion toxicology and TK study in male cynomolgus monkeys administered odronextamab was conducted (REGN2281-TX-13025). Complete necropsies were performed on the monkeys at the end of the 12-week observation period (Table 3).

Table 3: Single-Dose Toxicology (Study REGN2281-TX-13025)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Dosing Frequency	Doses (mg/kg)	Gender and No. Per Group	Noteworthy Findings
Cynomolgus monkey (*Macaca fascicularis)*	IV infusion Vehicle: (1x DPBS, pH 7.2) Control Article: 0.9% sodium chloride	once	1	3 males/group	• Drug-related B cell decrease in peripheral blood and lymphoid organs. • Transient increase in cytokine levels (TNFα, IL-2, IL-6, and IFN-γ) and transient decrease of T cells. • One animal humanely euthanized on Study Day 68 following consecutive days of liquid feces (positive for Campylobacter), dehydration and low food consumption. This animal had multiorgan inflammation and the associated, moribund condition was likely the result of an infection attributable to drug induced B cell depletion.

DPBS, Dulbecco's phosphate-buffered saline; IFN, interferon; IL, interleukin; IV, intravenous; NOAEL, no observable adverse effect level; TNF tumor necrosis factor.
[a] The NOAEL is underlined.

In this study, a single IV infusion of 1 mg/kg odronextamab to male cynomolgus monkeys was well tolerated for the duration of the 12-week observation period. No test article-related alterations in body weight, food consumption, neurobehavioral signs, body temperature, respiration rate, heart rate, hemoglobin saturation (measured by pulse oximetry), or blood pressure parameters were noted.

The no observable adverse effect level (NOAEL) for odronextamab is considered to be 1 mg/kg following single-dose IV administration since the test article-related findings are consistent with the expected pharmacology of B cell depletion and as such, not considered adverse.

4.3.2. 4-Week Repeat-Dose Intravenous Infusion Toxicology and Toxicokinetic Study with Odronextamab in Cynomolgus Monkeys Followed by a 12-Week Recovery Phase (REGN1979-TX-13091)

The in vivo safety profile and TK of odronextamab were evaluated during a 4-week repeat-dose, GLP compliant toxicology study in male and female cynomolgus monkeys

(REGN1979-TX-13091). Complete necropsies were performed at the end of the 4-week dosing phase (primary necropsy: 3 animals/sex/group) or at the end of the 12-week recovery phase (recovery necropsy: 3 animals/sex/group); selected organs were weighed, and tissues were examined macroscopically and microscopically. The noteworthy findings are summarized in Table 4 and Table 5.

Table 4: Repeat Dose Toxicology Study (REGN1979-TX-13091)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Dosing Frequency	Doses (mg/kg)	Gender and No. Per Group	Noteworthy Findings
Cynomolgus monkey (*Macaca fascicularis*)	IV infusion (10 mM histidine, 10% [w/v] sucrose, 0.1% [w/v] polysorbate 80, pH 5.8)	Once weekly for 4 weeks (total of 5 doses)	0, 0.01, 0.1, or 1	6 animals/ sex/group[b]	• Drug-related B cell decrease in peripheral blood and lymphoid organs. • Transient increase in cytokine levels (TNFα, IL-2, IL-6, and IFN-γ) and transient decrease of T cells after first dose only. • Vomit/emesis observed in some animals given 1 mg/kg after the first dose. • During the 12-week recovery period, 3 animals were humanely euthanized due to rapid deterioration following consecutive days of low food consumption, hunched posture body weight loss and/or liquid feces. Notable clinical pathology findings included increased CRP and neutrophils; decreases of lymphocytes in B cell regions of lymphoid organs and acute gastritis (2 animals). These findings are consistent with opportunistic infection resulting from robust and prolonged depletion of B cells. One animal (No. I08923M) given 1 mg/kg had inflammation in liver (portal) and bile-duct; clinical pathology did not indicate liver was a potential target organ. Inflammatory lesions in the liver of this animal considered most likely a consequence of the expected pharmacologic effects of odronextamab, rather than organ specific toxicity.

IFN, interferon; IL, interleukin; IV, intravenous; NOAEL, no observable adverse effect level; TNF tumor necrosis factor.

[a] The NOAEL is underlined.
[b] A subset of animals (3 animals/sex/group) were sacrificed at the end of the dosing period and the remaining animals (3 animals/sex/group) were maintained for 12 weeks.

During the recovery phase, 3 animals were euthanized at an unscheduled time-point due to rapid deterioration following consecutive days of low food consumption and body-weight loss. The changes are described below (Table 5).

Table 5: Description of Unscheduled Euthanasia (REGN1979-TX-13091)

Group (Animal Number)	Study Day	Clinical Pathology on Day of Euthanasia	Significant Clinical Observations/Pathology Findings
0.01 mg/kg (#8945 F)	47	Unable to collect	• Thin body condition; weight loss • Decreased B cells in multiple lymphoid organs • Marked epithelial atrophy of the stomach
1 mg/kg (#8927 M)	51	↑CRP, ↑neutrophils, and ↓albumin	• Thin body condition; weight loss • Decreased B cells in multiple lymphoid organs
1 mg/kg (#8951 F)	75	↑CRP, ↑neutrophils, and ↓albumin	• Thin body condition; weight loss • Decreased B cells in multiple lymphoid organs

CRP, C-reactive protein

Inflammation and generally deteriorating body condition are consistent with opportunistic infection resulting from robust and prolonged depletion of B cells. Similar effects were observed during the single-dose exploratory toxicology study (REGN2281-TX-13025) in which 1 animal administered a single 1 mg/kg IV dose of odronextamab was electively euthanized on day 68 following consecutive days of liquid feces that were positive for *Campylobacter*.

In summary, IV infusion of odronextamab QW for 4 weeks (5 total doses) was tolerated in cynomolgus monkeys at DLs up to 1 mg/kg. There were no odronextamab-related effects on body temperature, blood pressure, respiration rate, blood oxygen saturation, heart rate, neurological, ophthalmic, or ECG endpoints. Three animals were humanely euthanized during the recovery period. The findings in these animals were consistent with opportunistic infection, an expected consequence of the pharmacologic effects of odronextamab and sustained B cell depletion. The NOAEL for odronextamab is considered to be 1 mg/kg.

4.3.3. 16-Week Repeat-Dose Intravenous Infusion Toxicology and Toxicokinetic Study with Odronextamab in Cynomolgus Monkeys Followed by a 22-Week Recovery Phase (R1979-TX-17190)

Male and female cynomolgus monkeys received QW IV infusions of 0.1 mg/kg or 1 mg/kg odronextamab for 16 weeks (total of 17 doses). The concurrent control group received control article on a comparable regimen. A subset of animals was sacrificed 3 days after the last dose. The remaining animals were maintained for at least a 14-week dose-free recovery period.

Twelve animals (6 during the dosing period and 6 during the recovery period) administered 0.1 or 1 mg/kg/dose were electively euthanized early between day 77 of the dosing period and day 93 of the recovery period due to deteriorating body conditions. All of these animals had

pharmacological B cell depletion in the peripheral blood and decreased lymphoid cellularity at the time of unscheduled necropsy. The moribund condition of 10 animals was attributed to digestive system inflammation, noted in the gastrointestinal tract, gallbladder, and/or pancreas, and the moribund condition of 2 animals was attributed to jejunal intussusception/obstruction or general debilitation. Clinical observations, clinical pathology, and/or anatomic pathology findings in these animals were consistent with presumed secondary opportunistic infection associated with robust and sustained B cell depletion. All other remaining animals survived to their scheduled necropsy.

Odronextamab-related findings were consistent with expected pharmacology of B cell depletion or secondary effects related to that pharmacological B cell depletion. Also, administration of odronextamab was associated with transient increase in proinflammatory plasma cytokines (IL-6, IFN-γ, and TNF-α), a decrease in T lymphocytes and T cell activation following the first dose only. Increase in cytokines was generally correlated with clinical observations of hunched posture, emesis, hypoactivity, recumbency, vomitus, non-formed feces, and/or low food consumption on day 1. Consistent with presumed infections, clinical observations included fecal abnormalities (discolored, mucoid, non-formed, and/or liquid), body-weight losses, decreased food consumption, dehydration, hypoactivity, and/or thin body conditions which often warranted veterinary treatments. Eight animals administered 0.1 mg/kg/dose or 1 mg/kg/dose had infections confirmed by bacteriology (often noted from fecal cultures) and/or by veterinarian observations. Evidence supportive of intestinal and bacterial infection included Campylobacter overgrowth--in fecal cultures collected from 4 animals, and generally, concomitant urinary bladder and kidney pelvis mixed-cell inflammation and/or intestinal mixed-cell inflammation was associated with gall bladder, liver ductal and portal, pancreatic ductal mixed-cell inflammation. Anterior and posterior segment intraocular inflammation was noted in 1 animal each administered 0.1 mg/kg/dose and 1 mg/kg/dose on day 96 of the recovery phase that was not associated with microscopic correlates and were partially resolved by the next examination on day 102 of the recovery phase. Suppression of the anti-Keyhole Limpet Hemocyanin IgM and IgG responses was also observed following administration of odronextamab at ≥0.1 mg/kg/dose consistent with the pharmacology of odronextamab and associated immune suppression. Clinical pathology effects consistent with pharmacology of odronextamab included decreased white blood cell (WBC) and lymphocyte counts and globulin concentration.

Changes consistent with inflammation/infiltrate secondary to presumed infection and/or evidence of general debilitation included the following:

- Decreased creatinine kinase activity and cholesterol
- Increased CRP and fibrinogen
- Increased triglyceride concentration, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and/or gamma glutamyl transferase activities and total bilirubin concentration
- Prolonged activated partial thromboplastin time, decreased red blood cell (RBC) mass (RBC count, hemoglobin concentration, and/or hematocrit) and variable effects on reticulocyte count RBC
- Increased WBC and neutrophil counts, decreased eosinophil count

- Increased urea nitrogen, creatinine, and/or phosphorus concentrations
- Decreased sodium and chloride concentrations

Direct odronextamab-related pathology findings were decreased follicular lymphocytes (B cells) in the spleen, lymph nodes, gut-associated lymphoid tissue/Peyer's patch, and stomach mucosa. Mixed-cell inflammation and/or an increase in the incidence and/or severity of mixed and/or mononuclear cell infiltrates of several tissues including gastrointestinal tract, liver, and gall bladder, were consistent with secondary effects of B cell depletion and presumed opportunistic infections.

Increase in cytokines on day 1 and associated clinical signs, acute and transient decrease/activation of T-lymphocyte, sustained pharmacological depletion of B cells, associated anatomic pathology findings in lymphoid tissues, and presumed infections are consistent with what was previously reported in the 4-week repeat-dose toxicology study in cynomolgus monkeys.

4.3.4. Single-Dose Intravenous and Subcutaneous Toxicology and PK Study in Cynomolgus Monkeys With an up to 8-Week Recovery Period (R1979-TX-18196).

This study consisted of a single-dose phase (Phase 1) and an escalating-dose (step-up dosing) phase (Phase 2). Female cynomolgus monkeys in the single-dose phase received a single SC dose of 0.1 mg/kg or 1 mg/kg odronextamab or a single IV dose of 1 mg/kg. The concurrent control group received control article (formulation vehicle) IV and SC on a comparable regimen. Female monkeys in the subsequent escalating-dose phase received escalating IV or SC doses of 1, 25, and 100 mg/kg odronextamab. In each phase, a subset of animals was sacrificed 7 days after a single dose or 7 days after the third dose in a step-up regimen. The remaining animals were maintained for an additional 7 weeks following a single dose or the last (third) dose.

All animals survived to their scheduled sacrifice, although 2 animals assigned to the Phase 1 of the study were considered in moribund condition and 1 animal was in poor condition on the day of scheduled sacrifice on day 8 of the dosing period. The most notable clinical observations are consistent with those described in study REGN1979-TX-13091 and included abnormal fecal observations (non-formed and/or liquid feces), which also led to decreased body weight and thin condition for some animals and was likely due to suspected infection secondary to sustained B cell depletion. Dose-dependent increases in pro-inflammatory plasma cytokines generally correlated with clinical observations of non-formed feces, vomiting, elevated temperature, and/or skin discoloration in animals administered 1 mg/kg. T cell activation also correlated with increases in cytokines, which was noted following the first dose only. Clinical pathology effects included decreased lymphocyte counts and globulin concentration. Other changes in clinical pathology parameters consisted of minimal increases in cholesterol concentration or were considered secondary to gastrointestinal alterations/inflammation (accompanied by clinical observations of watery/liquid/non-formed feces) or poor condition. These changes included: increased neutrophil, basophil, large unstained cell, WBC counts, and CRP concentration (inflammation); decreased albumin, total protein, calcium (secondary to decreased albumin concentrations), sodium, chloride, and potassium concentrations (gastrointestinal loss); and increased urea nitrogen urine-specific gravity (dehydration). Changes during the recovery period

were noted in individual animals and included increased ALT, triglyceride concentration, and ALP activity. These changes were of unknown mechanism and were noted in the absence of a microscopic correlate. Direct odronextamab-related pathology findings consisted of decreased follicular lymphocytes (B cells) in the spleen, lymph nodes, gut-associated lymphoid tissue (GALT)/Peyer's patch, and the medulla of the thymus. There were no drug-related macroscopic or microscopic findings at the IV or SC injection sites, indicating injection site tolerance.

4.3.5. Reproductive and Development Toxicity

Reproductive and developmental toxicology studies have not been conducted.

4.3.6. Local Tolerability

Evaluation of local tolerability was performed as part of repeat-dose toxicology studies in monkeys following IV infusion or SC injection at doses up to 1 mg/kg or in a step-up regimen via the same routes at doses of 1 mg/25 mg/100 mg/kg (REGN1979-TX-13091 and R1979-TX-18196). There were no adverse clinical, macroscopic or microscopic changes evident at sites of administration, up to the highest DL tested indicating injection site tolerance.

4.3.7. Other Toxicity Studies

GLP ex vivo tissue cross-reactivity studies (REGN1979-TX-13092 and R1979-TX-18121) with biotinylated odronextamab were conducted using human (adult and fetal) and monkey tissues (Table 6). A biotinylated human IgG4 antibody that does not bind monkey or human CD3 or CD20 was used as a negative isotype control. A negative tissue control was also included and consisted of cryosections of HEK293 cells. Positive tissue controls included cryosections of CD3-expressing Jurkat cells and CD20-expressing Raji cells, as well as an ancillary tissue control consisting of human tonsil (mononuclear leucocytes).

Table 6: Tissue Cross-Reactivity Study REGN1979-TX-13092 and R1979-TX-18121

Species/ Strain	Method of Administration (Vehicle/Formulation)	Dosing Frequency	Doses (mg/kg)	Gender and No. Per Group	Noteworthy Findings
Normal human (adult and fetal) and cynomolgus monkey (*Macaca fascicularis)* tissues	NA	NA	2 and 10 µg/mL	NA	Expected staining of mononuclear leukocytes based on known expression of CD3 by T cells and CD20 by B cells in human and cynomolgus monkey tissues.

NA = not applicable

All staining in this study represented expected reactivity with the target antigens, and no unanticipated cross-reactivity of the test article was observed.

5. EFFECTS IN HUMANS

Unless stated otherwise, all results presented in this section refer to the data cutoff date of 18 Sep 2022.

As of the data cutoff date, a total of 3 clinical studies with odronextamab are being conducted: the first-in-human (FIH) phase 1 study R1979-HM-1333 and the phase 2 study R1979-ONC-1625 with odronextamab monotherapy, and the phase 1 study R1979-ONC-1504 of odronextamab in combination with the anti-PD-1 antibody cemiplimab (Table 7).

Table 7: Overview of the Ongoing Regeneron-Sponsored Clinical Studies with Odronextamab

Study Number/ Phase	Title	Study Objectives	Planned Number of Patients	Approximate Duration on Study (Treatment and Follow-up)	Status
R1979-HM-1333/ Phase 1	An open-label, multi-center phase 1 study to investigate the safety and tolerability of REGN1979, an anti-CD20 x anti-CD3 bispecific monoclonal antibody, in patients with CD20+ B cell malignancies previously treated with CD20-directed antibody therapy	Primary: to assess safety, tolerability, and DLTs of odronextamab in patients with B-NHL and CLL (IV administration) and B-NHL (SC administration); odronextamab concentrations in the expansion cohorts of aggressive lymphoma (excluding patients with prior CAR-T therapy) and FL Grade 1-3a; antitumor activity of odronextamab in the DLBCL after failure of CAR-T therapy expansion cohort.	298 patients	Patients are being treated until the time of disease progression or other protocol-defined reasons for treatment discontinuation. Patients who have discontinued treatment for reasons other than disease progression are to be followed for safety and efficacy until study discontinuation. After study discontinuation, patients are continued to be followed (remotely) for survival information.	Ongoing
R1979-ONC-1504/ Phase 1	A phase 1 study to assess safety and tolerability of REGN1979, an anti-CD20 x anti-CD3 bispecific monoclonal antibody, and REGN2810, an anti-programmed death-1 monoclonal antibody, in patients with B cell malignancies	Primary: To assess safety, tolerability, and DLT of cemiplimab monotherapy in patients with lymphoma (B-NHL and HL) and in combination with odronextamab in patients with B-NHL.	172 patients total	The study treatment period ranges from 9-12 months for combination odronextamab and cemiplimab study arms and 6 to 12 months for the other study arms. The follow-up period is 6 months.	Ongoing
R1979-ONC-1625/ Phase 2	An open-label study to assess the anti-tumor activity and safety of REGN1979, an anti-CD20 x anti-CD3 bispecific antibody, in patients with relapsed or refractory B-NHL	Primary: to assess anti-tumor activity of odronextamab monotherapy as measured by the ORR according to the Lugano Classification of response in malignant lymphoma (Cheson, 2014) and as assessed by independent central review (ICR) in each of the 5 disease-specific cohorts.	512 patients	Patients are being treated until the time of disease progression or other protocol-defined reason for treatment discontinuation. Patients who have discontinued treatment for reasons other than disease progression are to be followed for safety and efficacy until study discontinuation. After study discontinuation, patients are continued to be followed (remotely) for survival information.	Ongoing

B-NHL; B cell non-Hodgkin lymphoma; CAR-T, Chimeric antigen receptor T cell; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; DLT, dose-limiting toxicity; FL, follicular lymphoma; HL, Hodgkin lymphoma; IV, intravenous, ORR, overall response rate; SC, subcutaneous.

5.1. Study Designs and Enrollment

A total of 571 patients received odronextamab with 539 patients treated with odronextamab monotherapy in the 3 ongoing studies, and 32 patients treated with odronextamab in combination with cemiplimab in study R1979-ONC-1504.

5.1.1. R1979-HM-1333

5.1.1.1. Study Design

Study R1979-HM-1333 is an ongoing, FIH, open-label, multicenter, dose-finding and expansion study of odronextamab monotherapy in patients with CD20+ B cell malignancies (B-NHL and CLL) previously treated with anti-CD20 antibody therapy with both IV (Part A) and SC (Part B) administration. The primary objective of the study is presented in Table 7.

In Part A, dose escalation followed a traditional 3+3 design with 3 to 6 patients per dose level (DL) for patients with B-NHL and a modified 3+3 with accelerated titration component with 1 to 6 patients per DL for patients with CLL. Patients were treated at doses from 0.03 mg up to 320 mg with a step-up regimen (initial and intermediate doses in applicable DL), and QW full dose, with dose increases contingent on adequate tolerability of the previous lower dose.

Part A of the study is ongoing with enrollment into the expansion cohort for patients with DLBCL following failure of CAR-T therapy at a modified step-up regimen of 0.7 mg/4 mg/20 mg (as of protocol amendment 16), 160 mg QW dose through week 12, followed by a 320 mg every 2 weeks (Q2W) maintenance dose. If a patient demonstrates a CR and shows a durable response for at least 9 months, the frequency of the 320 mg maintenance dose will be decreased to every 4 weeks (Q4W) until disease progression or treatment discontinuation. Patients must have received the assigned full QW dose at the Q2W dosing schedule for at least 3 preceding doses before switching from Q2W to Q4W dosing.

In Part B of the study, the SC administration of odronextamab in patients with FL Grades 1-3a and DLBCL will be evaluated and will include a dose finding portion that follows the Bayesian Optimal Interval design with a 28-day dose-limiting toxicity (DLT) observation period to assess the safety of odronextamab and to select a recommended dose regimen for the expansion cohorts. Patients will receive SC odronextamab at the assigned dose in 21-day cycles. Cycle 1 will include weekly step-up doses until the step-up regimen is completed. The step-up regimen will include an initial dose and 2 intermediate doses (hereafter called intermediate dose-1 and intermediate dose-2). Step-up dosing in cycle 1 will be followed by treatment cycles at full dose, every 21 days, until the time of disease progression or other protocol-defined reason for treatment discontinuation. During the treatment period, the dosing regimen (frequency of dosing) is variable by cohort.

5.1.1.2. Study Enrollment

A total of 178 patients have been enrolled and received IV odronextamab monotherapy (164 patients in B-NHL cohort and 14 patients in CLL cohort). No patients received SC odronextamab at the time of the data cutoff date.

Among the 178 patients treated with odronextamab, 12 (6.7%) patients with B-NHL were on treatment and 166 (93.3%) patients had completed or discontinued study treatment.

The breakdown by subtype of patients treated with odronextamab is summarized in Table 8.

Table 8: Study Enrollment of Odronextamab Monotherapy (IV) in Phase 1 Study R1979-HM-1333

Study Entry and Initial Diagnosis	< 5mg (N=41)	≥ 5 to ≤ 12mg (N=19)	≥ 18 to ≤ 40mg (N=21)	80mg (N=15)	160mg (N=73)	320mg (N= 9)	Total (N=178)
CLL Cohort	14 (34.1%)	0	0	0	0	0	14 (7.9%)
Chronic lymphocytic leukemia	13 (31.7%)	0	0	0	0	0	13 (7.3%)
Hairy cell leukemia	1 (2.4%)	0	0	0	0	0	1 (0.6%)
B-NHL cohort	27 (65.9%)	19 (100%)	21 (100%)	15 (100%)	73 (100%)	9 (100%)	164(92.1%)
Diffuse Large B-cell Lymphoma	15 (36.6%)	11 (57.9%)	11 (52.4%)	6 (40.0%)	55 (75.3%)	5 (55.6%)	103 (57.9%)
Follicular Lymphoma 1-3a	8 (19.5%)	5 (26.3%)	8 (38.1%)	6 (40.0%)	11 (15.1%)	3 (33.3%)	41 (23.0%)
Mantle cell Lymphoma	3 (7.3%)	1 (5.3%)	1 (4.8%)	0	6 (8.2%)	1 (11.1%)	12 (6.7%)
Marginal zone Lymphoma	1 (2.4%)	1 (5.3%)	1 (4.8%)	3(20.0%)	0	0	6 (3.4%)
Other	1 (5.3%)	1 (5.3%)	0	0	1 (1.4%)	0	2 (1.1%)

B-NHL, B cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia.
Data cutoff date: 18 Sep 2022.

5.1.2. R1979-ONC-1625

5.1.2.1. Study Design

Study R1979-ONC-1625 is an ongoing, phase 2, multi-cohort, multicenter, open-label study to assess the anti-tumor activity and safety of odronextamab in patients with R/R B-NHL with prior systemic therapy. The primary objective of the study is presented in Table 7.

The study consists of 5 disease-specific cohorts (FL Grade 1-3a, DLBCL, MCL, MZL, and other B-NHL), each with independent parallel enrollment, enrolling up to 512 patients across the 5 disease-specific cohorts. The treatment duration comprises 12 QW doses followed by Q2W dosing until the time of disease progression or other protocol-defined reason for treatment discontinuation. Odronextamab is administered as IV monotherapy at an initial dose, followed by intermediate dose(s) as applicable, followed by a full dose QW based on cohort assignment. The step-up regimen has been revised to 0.7 mg/4.0 mg/20 mg as of global protocol amendment 4, Japan protocol amendment 2, and China protocol amendment 2. In addition, if a patient has demonstrated a CR and shows a durable response for at least 9 months after the initial determination of CR, then the frequency of study drug administration at the assigned dose will be decreased from Q2W to Q4W intervals, based on local investigator's evaluation. Patients must have received the assigned full QW dose at the Q2W dosing schedule for at least 3 preceding doses

before switching from Q2W to Q4W dosing. Patients will be followed for efficacy assessments until the time of disease progression or start of non-protocol anti-lymphoma therapy, whichever is earlier.

5.1.2.2. Study Enrollment

As of the cutoff date of 18 September 2022, a total of 360 patients have been treated with odronextamab monotherapy, with 114 (31.7%) patients on treatment and 246 (68.3%) patients discontinued treatment.

The breakdown by subtype of patients treated with odronextamab is summarized in Table 9.

Table 9: Study Enrollment of Odronextamab Monotherapy in Phase 2 Study R1979ONC-1625

Study Entry/Subtype	80 mg QW/ 160 mg Q2W (N=149)	160 mg QW/ 320 mg Q2W (N=178)	320 mg QW/ 320 mg Q2W (N=33)	Total (N=360)
FL Grade 1-3a	130 (87.2%)	0	0	130 (36.1%)
MZL	19 (12.8%)	0	0	19 (5.3%)
MCL	0	14 (7.9%)	0	14 (3.9%)
DLBCL	0	140 (78.7%)	33 (100%)	173 (48.1%)
Other B-NHL	0	24 (13.5%)	0	24 (6.7%)

B-NHL, B cell Non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.
Note: Full dose for FL Grade 1-3a, MZL is 80 mg QW/160 mg Q2W
Full dose for DLBCL (arm 1), MCL and other B-NHL is 160 mg QW/320 mg Q2W
Full dose for DLBCL (arm 2) is 320 mg QW/320 mg Q2W
Data cutoff date: 18 Sep 2022.

5.1.3. R1979-ONC-1504

5.1.3.1. Study Design

Study R1979-ONC-1504 is a phase 1, open-label, multicenter, dose-escalation study with multiple dose escalation and expansion arms in patients with B cell malignancies. Odronextamab is administered in combination with REGN2810 (also known as cemiplimab) in patients with B-NHL and Hodgkin Lymphoma. Prior to protocol amendment 4, odronextamab was administered as monotherapy to patients with ALL. In protocol version 4, the protocol was amended to remove the odronextamab monotherapy arm in patients with ALL. Patients may also receive cemiplimab alone.

Each dose escalation arm includes a different IV odronextamab DL. Within each DL, each patient receives odronextamab as an initial dose, an intermediate dose, and a higher QW (previously referred to as step-up or nominal dose); odronextamab dose increases for each patient are

contingent on adequate tolerability of the previous lower dose. The total treatment period is up to 12 months, and the follow-up period is 6 months.

Patients with B-NHL receive odronextamab in combination with cemiplimab. Cemiplimab is administered as an IV infusion of 3 mg/kg for all DLs (except DL-2 where the cemiplimab dose is 1 mg/kg), over 30 minutes Q2W for 24 doses in 48 weeks.

The primary objective of the study is presented in Table 7.

5.1.3.2. Study Enrollment

A total of 32 patients with B-NHL were treated with odronextamab in combination with 3 mg/kg cemiplimab at different DLs. A single patient with ALL received odronextamab monotherapy in study R1979-ONC-1504.

All 32 patients with B-NHL have discontinued study treatment, with 31 patients discontinuing the study, and 1 patient completing the study treatment. The disposition of the patients treated with odronextamab/cemiplimab combination therapy is summarized in Table 10. The patient with ALL also discontinued treatment.

Safety data from patients who received cemiplimab monotherapy treatment in study R1979-ONC-1504 are included in the Cemiplimab Investigator's Brochure.

Table 10: Enrollment of Odronextamab in Combination with Cemiplimab in Phase 1 Study R1979-ONC-1504

	Odronextamab plus Cemiplimab 3 mg/kg		
Study Entry and Initial Diagnosis	**< 5 mg (N=9)**	**5-12 mg (N=23)**	**Total (N=32)**
B-NHL			
Diffuse Large B cell lymphoma	6 (66.7%)	19 (82.6%)	25 (78.1%)
Follicular lymphoma	1 (11.1%)	0	1 (3.1%)
Mantle cell lymphoma	1 (11.1%)	2 (8.7%)	3 (9.4%)
Primary mediastinal B cell lymphoma	1 (11.1%)	2 (8.7%)	3 (9.4%)

B-NHL, B cell non-Hodgkin lymphoma.
Data cutoff date: 18 Sep 2021.

5.2. Pharmacokinetics in Humans

5.2.1. Study R1979-HM-1333

Odronextamab was intravenously administered to patients as 1- to 4-hour infusions. The dose range evaluated was from 0.03 mg to 320 mg. The study consisted of 17 cohorts (17 dose levels) in the dose-escalation phase and 5 cohorts in the dose-expansion phase of Part A. At each DL of the dose-escalation phase, step-up doses were implemented as an initial dose at week 1 at all DLs, and an intermediate dose at week 2 from DL11 (1 mg/6 mg/12 mg) to DL17 (1 mg/20 mg/320 mg) prior to full doses. The step-up doses were given as split doses preferably over 2 consecutive days. In the dose expansion phase, the step-up doses were initially 1 mg at week 1 and 20 mg at week 2

in the 5 cohorts. They were then modified (as of protocol amendment 16) to 0.7 mg/4mg/20mg in the first 3 weeks to mitigate the incidence and severity of grade ≥3 CRS in patients with DLBCL who failed prior CAR-T therapy.

Blood samples were collected for odronextamab concentration measurement with dense sampling for drug concentration analysis during weeks 1 to 12, and with reduced frequency thereafter. Odronextamab concentrations in serum were measured using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 0.003 mg/L.

Preliminary PK analysis was performed with available data from Part A. Generally, the odronextamab concentrations increased with increasing dose and exhibited non-linear PK properties particularly at doses less than 80 mg. The concentration-time profiles by DLs in patients with B-NHL were presented in the previous versions of the Odronextamab Investigator Brochure. Summary statistics of available odronextamab exposure data from patients with DLBCL who failed prior CAR-T therapy is provided in Table 11.

Table 11: Mean (±SD) Total Odronextamab Concentrations in Serum as Intravenous Administration in Patients with DLBCL who Failed Prior CAR-T Treatment (Dose Expansion Cohort, Study R1979-HM-1333)

Cohort n	Conc. (mg/L)	Week 1		Week 2		Week 3		Week 4		Week 8		Week 12	
		pre	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}
DLBCL after CAR-T failure (original*) n=6-20	dose	1 mg		20 mg		160 mg QW		160 mg QW		160 mg QW		160 mg QW	
	Mean	0	0.14	0.028	3.43	0.84	32.2	12.8	56.8	64.7	105	75.8	116
	SD		0.055	0.021	1.38	0.57	17.1	9.94	19.8	25.2	40.0	31.7	49.0
DLBCL after CAR-T failure (modified*) n = 4-14	dose	0.7 mg		4 mg		20 mg QW		160 mg QW		160 mg QW		160 mg QW	
	Mean	0	0.152	0.023	0.709	0.158	8.03	3.87	42.6	47.4	90.7	98.5	133
	SD		0.056	0.015	0.235	0.108	16.0	8.59	17.3	21.0	32.4	33.3	45.5

*modified = modified step-up doses (0.7/4/20 mg) in weeks 1-3 prior to full doses; original=original step-up doses (1/20 mg) in weeks 1-2 prior to full doses. CAR-T, chimeric antigen receptor T-cell; C_{max}= maximal concentration post infusion; C_{min}= concentration prior to next dose; DLBCL= diffuse large B cell lymphoma; LLOQ= lower limit of quantification; Pre= prior to the first dose, QW= once weekly; SD= standard deviation. Concentrations at LLOQ were set to 0.

5.2.2. Study R1979-ONC-1625

Odronextamab was intravenously administered as 1- to 4-hour infusions to patients QW for 12 weeks followed by Q2W dosing until disease progression or discontinuation from the study. Summary statistics of available odronextamab exposure data from patients with FL (80 mg QW), DLBCL (160 mg QW), MZL (80 mg QW), MCL (160 mg QW) and other B-NHL subtypes (160 mg QW) in the first 12 weeks are provided in Table 12. Results indicated that at full doses administered at ≥ week 4, odronextamab exposures are similar to full doses in patients with different B-NHL subtypes. Odronextamab concentration-time profiles of FL and DLBCL in the first 12 weeks with the original (1/20 mg) and modified (0.7/4/20 mg) step-up doses are depicted

in Figure 1. Concentrations with the modified step-up doses in the first 3 weeks were lower than that of the original step-up doses but similar once the full doses were administered.

Over the dose range (0.03 mg -320 mg, IV) evaluated in study R1979-HM-1333 and study R1979-ONC-1625, there were greater-than-dose proportional increases in serum concentration of total odronextamab, and the PK was characterized as non-linear, governed by target-mediated disposition. The target-mediated phase was most prominent at lower systematic concentrations associated with doses <80 mg and at early treatment weeks (eg, weeks 1-4). At doses ≥80 mg and at later weeks, the odronextamab exposure increased proportionally to dose. To characterize PK properties of odronextamab, concentration data from studies R1979-HM-1333 and R1979-ONC-1625 were used to develop a preliminary population PK model. Results suggested that odronextamab exhibits nonlinear PK properties with concentration- and time-dependent elimination. Consistent with the descriptive analysis, the target-mediated clearance was dominant at systematic concentrations associated with doses <80 mg and at early treatment weeks. For doses of at least 80 mg, the PK becomes linear; it is expected that the washout period for odronextamab is approximately 90 days after the last steady state dose, based on a conservative estimate.

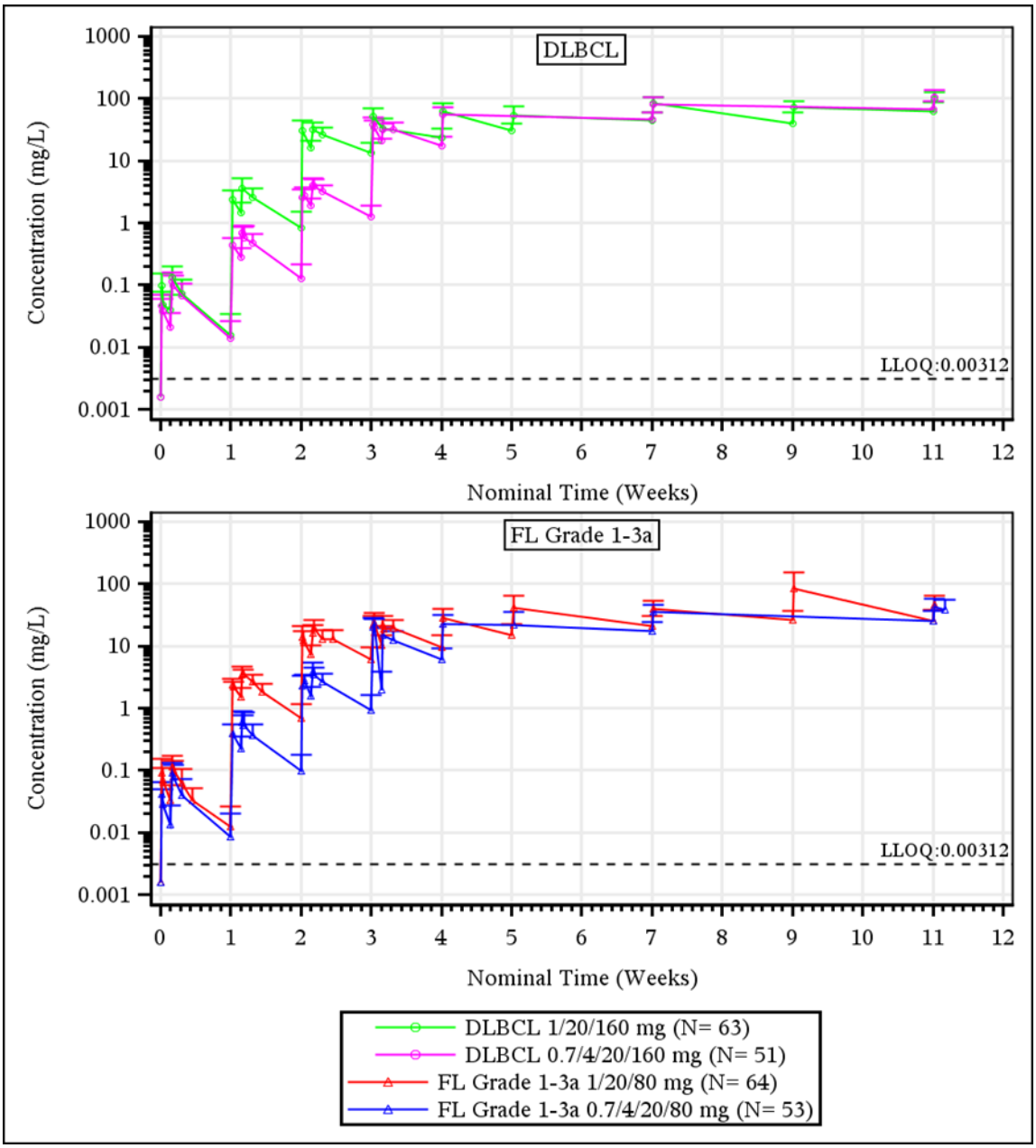
Table 12: Mean (±SD) Odronextamab Concentrations in Serum as Intravenous Administration in Patients with B-NHL (Study R1979-ONC-1625)

Cohort n	Conc. (mg/L)	Week 1		Week 2		Week 3		Week 4		Week 8		Week 12	
		pre	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}
FL 1-3a (original*) n=48-65	dose	1 mg		20 mg		80 mg QW		80 mg QW		80 mg QW		80 mg QW	
	Mean	0	0.723	0.310	3.13	0.742	12.9	4.21	21.5	20.6	37.4	24.3	45.1
	SD		4.27	0.174	4.96	2.12	8.74	3.79	10.9	10.3	15.2	13.5	19.1
FL 1-3a (modified*) n=26-54	dose	0.7 mg		4 mg		20 mg		80 mg QW		80 mg QW		80 mg QW	
	Mean	0	0.095	0.007	0.548	0.091	3.15	0.833	16.6	18.3	36.0	27.1	43.6
	SD		0.046	0.012	0.307	0.083	1.89	0.690	10.7	9.22	11.8	15.1	20.1
MZL (original) n=13-19	Mean	0	0.086	0.002	1.70	0.356	9.82	3.01	19.3	15.1	35.2	23.2	37.6
	SD		0.040	0.004	1.85	0.486	8.65	3.25	12.5	7.76	18.9	11.5	15.9
DLBCL (original) n=36-68	dose	1 mg		20 mg		160 mg QW		160 mg QW		160 mg QW		160 mg QW	
	Mean	0	0.131	0.014	3.08	0.695	29.4	11.0	46.2	45.0	82.9	61.8	97.1
	SD		0.071	0.018	1.77	0.695	17.1	7.37	23.5	15.5	23.9	24.8	27.5
DLBCL (modified) n=21-52	dose	0.7 mg		4 mg		20 mg		160 mg QW		160 mg QW		160 mg QW	
	Mean	0	0.118	0.013	0.659	0.122	3.80	1.20	37.3	46.2	77.8	67.0	107
	SD		0.043	0.013	0.234	0.090	1.45	0.67	14.9	14.7	24.1	23.1	30.7
MCL (original) n=7-14	Mean	0	0.071	0.008	2.29	0.326	19.3	6.44	35.3	38.8	69.5	59.3	87.8
	SD		0.053	0.011	1.62	0.348	17.2	6.69	18.9	17.7	19.6	28.2	33.1
Other NHL (original) n=8-14	Mean	0	0.098	0.013	3.11	0.668	25.5	10.9	43.8	26.5	67.4	61.8	99.4
	SD		0.039	0.015	1.78	0.598	17.7	9.10	26.2	20.2	35.8	42.2	43.1

Other NHL (modified) n=4-8	Mean SD	0	0.097 0.045	0.007 0.011	0.524 0.228	0.090 0.069	3.33 1.52	0.995 0.664	30.9 14.2	33.2 10.1	66.2 16.5	52.8 21.9	80.8 9.69

*modified**,** modified step-up doses (0.7/4/20 mg) in weeks 1-3 prior to full doses
B-NHL= B cell non-Hodgkin lymphoma; original, Cmin, concentration prior to next dose; Cmax , maximal concentration post infusion; DLBCL, diffuse large B cell lymphoma; original step-up doses (1/20 mg) in weeks 1-2 prior to full doses. FL, follicular lymphoma, LLOQ, lower limit of quantification; MCL, mantle cell lymphoma, MZL, marginal zone lymphoma; Pre, prior to the first dose, QW, once weekly; SD, standard deviation.
Concentrations at LLOQ were set to 0.

Figure 1: Mean Concentration (+SD) of Total Odronextamab in Serum by Nominal Time in the First 12 weeks in Patients with R/R DLBCL and R/R FL (Study R1979-ONC-1625)



DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; LLOQ= lower limit of quantitation
The mean concentration-time profiles were presented in a log scale. Regimen of each cohort is presented at the bottom of the plot. Concentrations below the LLOQ were set to LLOQ/2. Only included timepoints where n>1.

5.2.3 Study R1979-ONC-1504

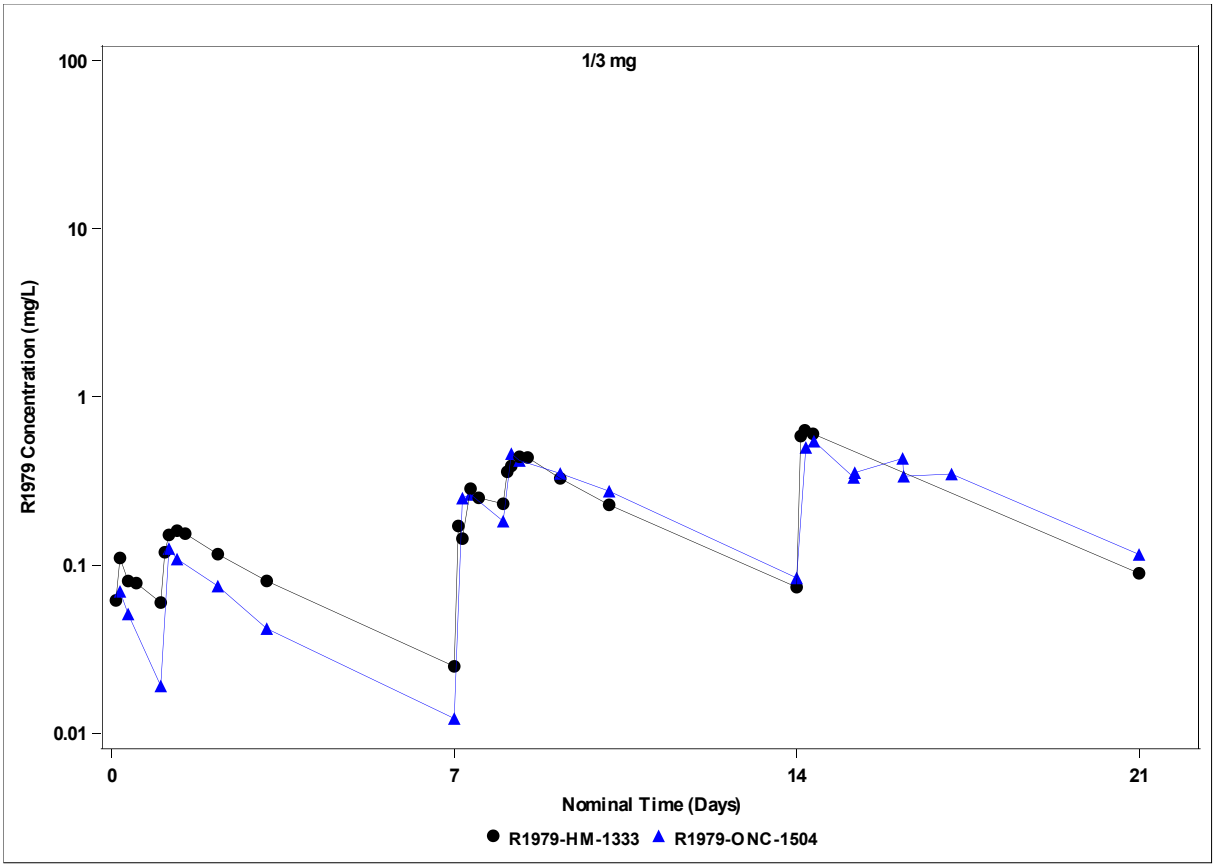
Odronextamab was intravenously administered to patients with B-NHL in combination with cemiplimab. Cemiplimab was administered at dosages of 1 mg/kg and 3 mg/kg Q2W as a

monotherapy, or at 3 mg/kg Q2W in combination with odronextamab to patients with B cell lymphoma.

Preliminary PK analysis for odronextamab was performed using the available data. At a given dosage, the odronextamab exposure levels were similar to those reported under monotherapy in study R1979-HM-1333.

Representations of odronextamab concentration-time profiles in combination with cemiplimab (Study R1979-ONC-1504) compared to monotherapy (Study R1979-HM-1333) are shown in Figure 2, indicating that in this relatively small dataset, odronextamab exposure was not affected by the co-administration with cemiplimab.

Figure 2: Cross-Study Comparison of Mean Odronextamab Concentration-Time Profiles Following IV Administration (QW) with Cemiplimab (Study R1979-ONC-1504) or without Cemiplimab (Study R1979-HM-1333)



PK, Pharmacokinetic(s); QW, once weekly.
Note: The blue line represents a mean PK profile of odronextamab when co-administered with cemiplimab (Study R1979-ONC-1504; n=3); the black line represents a mean PK profile of odronextamab when administered alone (Study R1979-HM-1333; n=3). Regimen (1/3 mg) is an initial dose of 1 mg (split to 2 x 0.5mg) followed by 3 mg in week 2 (split to 2 x 1.5mg) and week 3 (3mg 1 single infusion).

5.3. Immunogenicity

5.3.1. Study R1979-HM-1333

Immunogenicity against odronextamab is low. Among a total of 145 patients who had ADA information in the dose escalation and expansion phases (Part A), only 1 patient (0.7%) in DL4 (1 mg/2 mg) had treatment-emergent ADAs with low titer at the last visit of the 30-day safety follow-up.

5.3.2. Study R1979-ONC-1625

Among a total of 173 patients who had ADA information (all cohorts included), 5 patients (2.9%) had treatment emergent ADAs. The odronextamab exposures are similar in patients with positive or negative ADA measures.

5.3.3. Study R1979-ONC-1504

As of the data cutoff date, there is no new ADA information for the patients in this study.

5.4. Safety of Pooled Odronextamab Monotherapy Treatment Studies

5.4.1. Patient Disposition

Overall, 539 patients received odronextamab monotherapy treatment in all 3 studies. As of the data cutoff date 18 Sep 2022, 126 patients remained on treatment and 413 patients were off treatment (Table 13):

- Study R1979-HM-1333 (N=178): a total of 166 patients completed treatment during a per-protocol fixed treatment period and 12 patients remained as ongoing.
- Study R1979-ONC-1504 (N=1): the single patient with ALL had discontinued treatment.
- R1979-ONC-1625 (N=360): a total of 246 patients had discontinued treatment and 114 patients remained on treatment.

Table 13: Patient Disposition in Odronextamab Monotherapy Treatment

Disposition Status	**< 80 mg**	**80 mg**	**160 mg**	**320 mg**	**Total**
	(N=82)	**(N=164)**	**(N=251)**	**(N=42)**	**(N=539)**
Treatment Ongoing, n (%)	0	61 (37.2%)	61 (24.3%)	4 (9.5%)	126 (23.2%)
Off Treatment, n (%)	82 (100%)	103 (62.8%)	190 (75.7%)	38 (90.5%)	413 (76.6%)
Primary Reason for Treatment Discontinuation					
Progressive Disease	37 (45.1%)	34 (20.7%)	101 (40.2%)	20 (47.6%)	192 (35.6%)
Adverse Event	6 (7.3%)	18 (11.0%)	24 (9.6%)	4 (9.5%)	52 (9.6%)

Disposition Status	< 80 mg	80 mg	160 mg	320 mg	Total
	(N=82)	(N=164)	(N=251)	(N=42)	(N=539)
Death	3 (3.7%)	13 (7.9%)	25 (10%)	4 (9.5%)	45 (8.3%)
Physician Decision	4 (4.9%)	18 (11.0%)	14 (5.6%)	3 (7.1%)	39 (7.2%)
Subject Decision	8 (9.8%)	8 (4.9%)	6 (2.4%)	2 (4.8%)	24 (4.4%)
Withdrawal of Consent	0	6 (3.7%)	6 (2.4)	2 (4.8%)	14 (2.6%)
Other	5 (6.1%)	1 (0.6%)	2 (0.7%)	0	8 (1.5%)
Sponsor Decision	0	0	1 (0.4%)	0	1 (0.2%)
Ongoing in the Study, n (%)	3 (3.7%)	89 (54.3%)	81 (32.3%)	10 (23.8%)	183 (34.0%)
Off Study, n (%)	79 (96.3%)	75 (45.7%)	170 (67.7%)	32 (76.2%)	356 (66.0%)
Primary Reason for Study Discontinuation					
Progressive Disease	30 (36.6%)	20 (12.2%)	52 (20.7%)	11 (26.2%)	113 (21.0%)
Death	11 (13.4%)	19 (11.6%)	56 (22.3%)	8 (19%)	94 (17.4%)
Subject Decision	11 (13.4%)	19 (11.6%)	28 (11.2%)	5 (11.9%)	63 (11.7%)
Withdrawal of Consent	1 (1.2%)	0	2 (0.8%)	1 (2.4%)	4 (0.7%)
Physician Decision	3 (3.6%)	5 (3.0%)	6 (2.4%)	1 (2.4%)	15 (2.8%)
Adverse Event	1 (1.2%)	2 (1.2%)	2 (0.8%)	0	5 (0.9%)
Other	11 (13.4%)	7 (4.3%)	22 (8.8%)	4 (9.5%)	44 (8.2%)
Lost to Follow-Up	0	0	1 (0.4%)	0	1 (0.2%)

Data cutoff date: 18 Sep 2022

5.4.2. Treatment Exposure

Information on the treatment exposure to odronextamab monotherapy excluding retreatment of patients for studies R1979-HM-1333 and R1979 ONC 1625 (see Section 5.4.2.1 for treatment exposure including retreatment), is presented in Table 14 and Table 15. One patient who received odronextamab monotherapy in study R1979-ONC-1504 is not included.

Table 14: Odronextamab Treatment Exposure for study R1979-HM-1333 (Excluding Retreatment)

R1979-HM-1333	<5mg	≥5 to ≤12mg	≥18 to ≤40mg	80mg	160mg	320mg	Total
	(N=41)	(N=19)	(N=21)	(N=15)	(N=73)	(N=9)	(N=178)
Duration of exposure (weeks) [a]							
Mean (SD)	15.68 (20.86)	23.56 (23.55)	24.10 (12.41)	30.41 (22.82)	17.26 (18.97)	18.14 (12.23)	19.53 (19.66)
Median	6.14	11	25	27.29	10	13.14	13
Q1: Q3	4.00: 21.14	6.00: 37.00	13.43: 36.86	13.00: 37.14	4.14: 23.00	8.86: 22.86	5.00: 29.00

R1979-HM-1333	<5mg	≥5 to ≤12mg	≥18 to ≤40mg	80mg	160mg	320mg	Total
	(N=41)	(N=19)	(N=21)	(N=15)	(N=73)	(N=9)	(N=178)
Min: Max	2.0: 116.9	2.1: 100.3	2.1: 44.1	2.6: 98.9	0.7: 109.0	5.0: 37.0	0.7: 116.9
Number of Doses Administered							
Mean (SD)	7.7 (5.91)	14.7 (9.47)	19.7 (7.48)	22.2 (9.16)	14.2 (10.44)	15.9 (7.17)	14.2 (9.77)
Median	6	11	21	22	12	15	11
Q1: Q3	4.0: 10.0	7.0: 26.0	15.0: 27.0	16.0: 27.0	6.0: 20.0	11.0: 18.0	6.0: 21.0
Min: Max	1:27	2:27	2:29	6:45	1:50	7:27	1:50

Max, maximum; Min, minimum; Q, quartile; SD, standard deviation.
Duration of Treatment Exposure (weeks) = Minimum of [(A) (date of last odronextamab dose of core treatment- date of first odronextamab dose of core treatment + 14 days) or (B) (minimum of (date of clinical data cutoff or date of death) - date of first odronextamab dose of core treatment+1) or (C) ((minimum of (date of clinical data cutoff or date of first odronextamab dose of retreatment-1) - date of first odronextamab dose of core treatment+1)]/7
Data cutoff date: 18 Sep 2022.

Table 15: Odronextamab Treatment Exposure for study R1979-ONC-1625

R1979-ONC-1625	FL Grade 1-3a 80 mg	MZL 80 mg	MCL 160 mg	Other B-NHL 160 mg	DLBCL 160 mg	DLBCL 320 mg	Total
	(N=130)	(N=19)	(N=14)	(N=24)	(N=140)	(N=33)	(N=360)
Duration of Exposure (weeks)[a]							
Mean (SD)	35.23 (30.96)	58.69 (38.04)	44.99 (45.6)	29.57 (28.36)	23.01 (25.2)	39.34 (40.21)	32.10 (31.92)
Median	22.5	64.14	20.07	21.79	14.86	19	19.71
Q1: Q3	13.00: 54.57	25.43: 99.00	3.14: 99.43	8.43: 44.50	6.07: 26.93	12.86: 60.29	9.71: 47.07
Min: Max	0.4: 137.0	3.0: 113.0	0.1: 116.0	1.9: 108.3	0.9: 118.9	2.0: 124.9	0.1: 137.0
Number of Doses Administered							
Mean (SD)	22.72 (13.03)	31.37 (15.6)	24.21 (20.6)	18.96 (12.52)	16.59 (11.20)	23.12 (15.31)	20.64 (13.54)
Median	19	32	18	16	15	17	18
Q1: Q3	15.00: 35.00	21.00: 44.00	4.00: 43.00	10.50: 25.00	8.00: 21.00	14.00: 35.00	11.00: 29.00
Min: Max	1.0: 61.0	3.0: 52.0	1.0: 61.0	2.0: 52.0	1.0: 52.0	1.0: 54.0	1.0: 61.0

B-NHL, B-cell Non-Hodgkin Lymphoma; DLBCL, Diffuse large B cell lymphoma; FL, follicular lymphoma; Max, maximum; Min, minimum; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma; Q, quartile; SD, standard deviation;
[a] Duration of Treatment Exposure (weeks) = Minimum of [(A) (date of last odronextamab dose of core treatment- date of first odronextamab dose of core treatment + 14 days) or Minimum of (B) (date of clinical data cutoff or date of death) - date of first odronextamab dose of core treatment+1) or Minimum of (C) (date of clinical data cutoff or date of first odronextamab dose of retreatment-1) - date of first odronextamab dose of core treatment+1)]/7
[b] Actual Dose Intensity (mg/week) = Cumulative Dose Administrated/Duration of Exposure.Data cutoff date: 18 Sep 2021.

5.4.2.1. Patient Exposure (RETREATMENT)

A total of 9 patients (all from study R1979-HM-1333) received odronextamab monotherapy retreatment after the core treatment period. Seven of the 9 patients that received retreatment had B-NHL and 2 patients had CLL; all 9 patients discontinued retreatment. Patients in retreatment had a median duration of exposure of 8.0 weeks (range 4.0 weeks to 45.0 weeks). The total number of odronextamab doses per patient administered as retreatment was a median of 5 doses (range 3 to 26 doses).

5.4.3. Dose-Limiting Toxicities

Dose-limiting toxicities were evaluated in the phase 1 dose escalation study of R1979-HM-1333. One patient with hairy cell leukemia enrolled at DL3 (0.3/1 mg) in the CLL arm experienced DLTs of Grade 4 TLS and Grade 3 CRS (characterized by ALT increase, AST increase and hypotension) following initial dosing (0.15 mg) of odronextamab. These events resolved without sequelae upon treatment discontinuation. No other patients experienced DLTs as of the data cutoff date.

5.4.4. Treatment-Emergent Adverse Events

Treatment-emergent adverse events included all AEs that occurred during treatment and safety follow-up period (core treatment period). Among the 539 patients treated with odronextamab, TEAEs were reported in 535 (99.3%) patients. Of the 539 patients treated with odronextamab monotherapy, 73 patients were treated in dose escalation, 300 patients were treated with the 1/20 mg step-up regimen and 166 patients were treated with the modified (0.7/20/40 mg) regimen.

Frequency of Treatment-Emergent Adverse Events

The TEAEs reported were generally consistent with the MOA of odronextamab or the underlying malignancy. Tolerability was maintained with dose escalation as shown by cumulative TEAEs in DLs up to 320 mg of odronextamab.

Summaries of TEAEs experienced by patients treated with different doses of odronextamab monotherapy are provided in Table 16, Table 17, and Table 18 .

The most frequently reported TEAEs (by preferred term [PT]) in patients (≥15%) treated with odronextamab monotherapy (N=539) during the core treatment period are summarized in Table 19.

Table 16: Summary of Treatment-Emergent Adverse Events - Odronextamab Monotherapy

	< 80 mg	80 mg	160 mg	320 mg	Total
	(N=82)	(N=164)	(N=251)	(N=42)	(N=539)
Patients with any TEAE, n (%)	82 (100%)	164 (100%)	247 (98.4%)	42 (100%)	535 (99.3%)
Patients with any Severity Grade 3/4/5 TEAE, n (%)	67 (81.7%)	130 (79.3%)	198 (78.9%)	37 (88.1%)	432 (80.1%)

	< 80 mg	80 mg	160 mg	320 mg	Total
	(N=82)	(N=164)	(N=251)	(N=42)	(N=539)
Patients with any Serious TEAE, n (%)	48 (58.5%)	103 (62.8%)	149 (59.4%)	29 (69.0%)	329 (61.0%)
Patients who discontinued study treatment due to TEAEs, n (%)	7 (8.5%)	17 (10.4%)	25 (10.0%)	4 (9.5%)	53 (9.8%)
Patients who discontinued study treatment due to treatment-related TEAEs, n (%)	5 (6.1%)	10 (6.1%)	1 (7.6%)	3 (7.1%)	37 (6.9%)
Patients with at least one TEAE resulting in death, n (%)	4 (4.9%)	18 (11.0%)	27 (10.8%)	2 (4.8%)	51 (9.5%)
Patients with at least one treatment-related TEAE resulting in death, n (%)	3 (3.7%)	4 (2.4%)	8 (3.2%)	2 (4.8%)	17 (3.2%)

n, number of patients; TEAE, treatment-emergent adverse event.
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

Table 17: Summary of Treatment-Emergent Adverse Events – Monotherapy <80 mg, 160 mg, and 320 mg with 1/20 mg Step-up Regimen

	< 80 mg	80 mg	160 mg	320 mg	Total
	(N=9)	(N=102)	(N=147)	(N=42)	(N=300)
Patients with any TEAE, n (%)	9 (100%)	102 (100%)	146 (99.3%)	42 (100%)	299 (99.7%)
Patients with any Severity Grade 3/4/5 TEAE, n (%)	9 (100%)	87 (85.3%)	126 (85.7%)	37 (88.1%)	259 (86.3%)
Patients with any Serious TEAE, n (%)	7 (77.8%)	67 (65.7%)	95 (64.6%)	29 (69.0%)	198 (66.0%)
Patients who discontinued study treatment due to TEAEs, n (%)	2 (22.2%)	14 (13.7%)	19 (12.9%)	4 (9.5%)	39 (13.0%)
Patients who discontinued study treatment due to treatment-related TEAEs, n (%)	1 (11.1%)	8 (7.8%)	13 (8.8%)	3 (7.1%)	25 (8.3%)
Patients with at least one TEAE resulting in death, n (%)	1 (11.1%)	14 (13.7%)	15 (10.2%)	2 (4.8%)	32 (10.7%)
Patients with at least one treatment-related TEAE resulting in death, n (%)	1 (11.1%)	4 (3.9%)	5 (3.4%)	2 (4.8%)	12 (4.0%)

n, number of patients; TEAE, treatment-emergent adverse event.
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.

R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

Table 18: Summary of Treatment-Emergent Adverse Events – 0.7/4/20 mg Odronextamab Monotherapy Step-up Regimen

	80 mg	160 mg	Total
	(N=62)	(N=104)	(N=166)
Patients with any TEAE, n (%)	62 (100%)	101 (97.1%)	163 (98.2%)
Patients with any Severity Grade 3/4/5 TEAE, n (%)	43 (69.4%)	72 (69.2%)	115 (69.3%)
Patients with any Serious TEAE, n (%)	36 (58.1%)	54 (51.9%)	90 (54.2%)
Patients who discontinued study treatment due to TEAEs, n (%)	3 (4.8%)	6 (5.8%)	9 (5.4%)
Patients who discontinued study treatment due to treatment-related TEAEs, n (%)	2 (3.2%)	6 (5.8%)	8 (4.8%)
Patients with at least one TEAE resulting in death, n (%)	4 (6.5%)	12 (11.5%)	16 (9.6%)
Patients with at least one treatment-related TEAE resulting in death, n (%)	0	3 (2.9%)	3 (1.8%)

n, number of patients; TEAE, treatment-emergent adverse event.
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

Severity of Treatment-Emergent Adverse Events

A total of 432 of the 539 (80.1%) patients treated with odronextamab monotherapy experienced TEAEs assessed as Grade ≥3 (Table 19).

Grade ≥3 TEAEs reported in ≥5% of patients were Neutropenia (n =145, 26.9%), Anaemia (n =107, 19.9%), AST increase (n =37, 6.9%) and ALT increase (n =37, 6.9%), CRS (n =34, 6.3%).

Fifty-one (9.5%) patients treated with odronextamab monotherapy experienced 53 treatment-emergent events leading to death: 12 due to Coronavirus disease 2019 (COVID-19) (PTs, COVID-19 in 8 patients, COVID-19 pneumonia in 3 patients and SARS-CoV-2 test positive in 1 patient), Pneumonia (7 patients), Cardiac arrest (4 patients), Sepsis (4 patients), and *Pneumocystis jirovecii* pneumonia (1 patient). Pseudomonal sepsis, Toxoplasmosis, Cardio-respiratory arrest, Gastric perforation, Upper gastrointestinal hemorrhage, General physical health deterioration, CRS, Subarachnoid hemorrhage, TLS, Respiratory syncytial virus bronchitis, Interstitial lung disease , *Escherichia coli* sepsis, CMV infection reactivation, CMV pneumonia, Progressive multifocal leukoencephalopathy, RSV bronchitis, Systemic mycosis, Atrial fibrillation, Rectal hemorrhage, Multiple organ dysfunction syndrome, Hemophagocytic lymphohistiocytosis, Brain herniation, Metabolic disorder, Interstitial lung disease, and Hypotension were each experienced by 1 patient. Fatal events of Pneumonia and concurrent Sepsis were reported in 1 patient.

Table 19: Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and NCI-CTCAE Grade Experienced by ≥15% Patients (All Grades Total) during Core Treatment

Primary System Organ Class / Preferred Term	< 80 mg (N=82)		80 mg (N=164)		160 mg (N=251)		320 mg (N=42)		Total (N=539)	
	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5
Patients with any TEAE, n (%)	82 (100%)	67 (81.7%)	164 (100%)	130 (79.3%)	247 (98.4%)	198 (78.9%)	42 (100%)	37 (88.1%)	535 (99.3%)	432 (80.1%)
General disorders and administration site conditions	80 (97.6%)	7 (8.5%)	104 (63.4%)	11 (6.7%)	160 (63.7%)	26 (10.4%)	37 (88.1%)	4 (9.5%)	381 (70.7%)	48 (8.9%)
Pyrexia	69 (84.1%)	1 (1.2%)	59 (36.0%)	3 (1.8%)	110 (43.8%)	5 (2.0%)	28 (66.7%)	1 (2.4%)	266 (49.4%)	10 (1.9%)
Fatigue	30 (36.6%)	5 (6.1%)	32 (19.5%)	3 (1.8%)	47 (18.7%)	6 (2.4%)	12 (28.6%)	0	121 (22.4%)	14 (2.6%)
Chills	47 (57.3%)	1 (1.2%)	12 (7.3%)	0	29 (11.6%)	2 (0.8%)	11 (26.2%)	0	99 (18.4%)	3 (0.6%)
Immune system disorders	43 (52.4%)	5 (6.1%)	101 (61.6%)	9 (5.5%)	146 (58.2%)	18 (7.2%)	28 (66.7%)	5 (11.9%)	318 (59.0%)	37 (6.9%)
Cytokine release syndrome	42 (51.2%)	5 (6.1%)	94 (57.3%)	8 (4.9%)	140 (55.8%)	17 (6.8%)	27 (64.3%)	4 (9.5%)	303 (56.2%)	34 (6.3%)
Blood and lymphatic system disorders	48 (58.5%)	36 (43.9%)	94 (57.3%)	60 (36.6%)	134 (53.4%)	97 (38.6%)	25 (59.5%)	18 (42.9%)	301 (55.8%)	211 (39.1%)
Neutropenia[a]	22 (26.8%)	18 (22.0%)	71 (43.3%)	55 (33.0%)	74 (29.4%)	61 (24.3%)	13 (30.9%)	11 (26.2%)	180 (33.4%)	145 (26.9%)
Anaemia	27 (32.9%)	16 (19.5%)	52 (31.7%)	21 (12.8%)	99 (39.4%)	56 (22.3%)	18 (42.9%)	14 (33.3%)	196 (36.4%)	107 (19.9%)
Metabolism and nutrition disorders	43 (52.4%)	15 (18.3%)	92 (56.1%)	24 (14.6%)	136 (54.2%)	52 (20.7%)	30 (71.4%)	7 (16.7%)	301 (55.8%)	98 (18.2%)
Decreased appetite	12 (14.6%)	3 (3.7%)	29 (17.7%)	0	32 (12.7%)	1 (0.4%)	15 (35.7%)	1 (2.4%)	88 (16.3%)	5 (0.9%)
Gastrointestinal disorders	49 (59.8%)	7 (8.5%)	84 (51.2%)	5 (3.0%)	136 (54.2%)	20 (8.0%)	31 (73.8%)	5 (11.9%)	300 (55.7%)	37 (6.9%)
Diarrhoea	11 (13.4%)	1 (1.2%)	33 (20.1%)	0	50 (19.9%)	4 (1.6%)	9 (21.4%)	1 (2.4%)	103 (19.1%)	6 (1.1%)

Primary System Organ Class Preferred Term	< 80 mg (N=82)		80 mg (N=164)		160 mg (N=251)		320 mg (N=42)		Total (N=539)	
	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5
Nausea	22 (26.8%)	0	29 (17.7%)	1 (0.6%)	33 (13.1%)	1 (0.4%)	10 (23.8%)	1 (2.4%)	94 (17.4%)	3 (0.6%)
Investigations	58 (70.7%)	33 (40.2%)	83 (50.6%)	50 (30.5%)	130 (51.8%)	77 (30.7%)	27 (64.3%)	11 (26.2%)	298 (55.3%)	171 (31.7%)
Alanine aminotransferase increased	13 (15.9%)	3 (3.7%)	31 (18.9%)	17 (10.4%)	36 (14.3%)	12 (4.8%)	7 (16.7%)	5 (11.9%)	87 (16.1%)	37 (6.9%)
Aspartate aminotransferase increased	16 (19.5%)	4 (4.9%)	27 (16.5%)	14 (8.5%)	36 (14.3%)	15 (6.0%)	7 (16.7%)	4 (9.5%)	86 (16.0%)	37 (6.9%)
Respiratory, thoracic and mediastinal disorders	42 (51.2%)	11 (13.4%)	65 (39.6%)	15 (9.1%)	92 (36.7%)	20 (8.0%)	22 (52.4%)	3 (7.1%)	221 (41.0%)	49 (9.1%)
Cough	13 (15.9%)	0	25 (15.2%)	0	52 (20.7%)	0	8 (19.0%)	0	98 (18.2%)	0
Nervous system disorders	33 (40.2%)	1 (1.2%)	69 (42.1%)	11 (6.7%)	91 (36.3%)	16 (6.4%)	25 (59.5%)	2 (4.8%)	218 (40.4%)	30 (5.6%)
Headache	17 (20.7%)	0	36 (22.0%)	1 (0.6%)	26 (10.4%)	1 (0.4%)	12 (28.6%)	0	91 (16.9%)	2 (0.4%)
Injury, poisoning and procedural complications	34 (41.5%)	5 (6.1%)	72 (43.9%)	12 (7.3%)	71 (28.3%)	9 (3.6%)	13 (31.0%)	2 (4.8%)	190 (35.3%)	28 (5.2%)
Infusion related reaction	29 (35.4%)	4 (4.9%)	50 (30.5%)	7 (4.3%)	45 (17.9%)	3 (1.2%)	11 (26.2%)	1 (2.4%)	135 (25.0%)	15 (2.8%)
Psychiatric disorders	23 (28.0%)	0	34 (20.7%)	1 (0.6%)	54 (21.5%)	4 (1.6%)	17 (40.5%)	2 (4.8%)	128 (23.7%)	7 (1.3%)
Insomnia	11 (13.4%)	0	25 (15.2%)	0	37 (14.7%)	1 (0.4%)	10 (23.8%)	0	83 (15.4%)	1 (0.2%)

[a]Composite Terms (encompassing PT terms) - Neutropenia - (Neutrophil count decreased, Neutropenia)
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff: 18 Sep 2022.

5.4.4.1. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation

A total of 53 patients (9.8%) experienced TEAEs leading to odronextamab treatment discontinuation. Among these patients, TEAEs experienced by ≥2 patients were, Pneumonia (n=7, 1.3%), CRS (n=4, 0.7%), COVID-19 pneumonia (n=3, 0.6%), Encephalopathy (n=3, 0.6%), IRR (n=3, 0.6%). COVID-19, CMV infection reactivation, *Pneumocystis jirovecii* pneumonia, TLS, Fatigue, Myelodysplastic syndrome, AST increase, and Weight decreased were each experienced by 2 patients (0.4%). All events except 2 events of Encephalopathy, 1 event of Pneumonia, 1 event of COVID-19 pneumonia, 1 event of CMV infection reactivation, 1 event of Myelodysplastic syndrome and 1 event of CRS were not Grade ≥3.

5.4.4.2. Serious Treatment-Emergent Adverse Events

Among the 539 patients who received odronextamab monotherapy, serious TEAEs were reported in 329 (61.0%) patients. The serious TEAEs reported in ≥5% of patients were CRS (n=119, 22.1%), Pneumonia (n=42, 7.8%), and Pyrexia (n=30, 5.6%). A total of 241 (44.7%) patients experienced a serious TEAE ≥Grade 3. Serious TEAEs (Grade ≥ 3) experienced by ≥1% patients were Pneumonia (n=38, 7.1%), CRS (n=27, 5.0%), COVID-19 (n=23, 4.3%), COVID-19 pneumonia (n=12, 2.2%), *Pneumocystis jirovecii* pneumonia and Sepsis (n=11, 2.0% each), IRR (n=9, 1.7%), CMV reactivation (n=8, 1.5%), Encephalopathy and Hypotension (n=7, 1.3% each), Pulmonary embolism and CMV infection and Pneumonitis and Urinary tract infection (n=6, 1.1% each).

5.4.5. Summary of Treatment-Related Treatment-Emergent Adverse Events

Four hundred and ninety-one of 539 patients (91.1%) experienced at least 1 TEAE assessed by the investigator as being related to odronextamab treatment.

Frequency of Treatment-Related Treatment-Emergent Adverse Events

All treatment-related TEAEs experienced by ≥5% patients treated with odronextamab monotherapy are included in Table 20. Treatment-related TEAEs reported in ≥15% of patients were CRS (n=301, 55.8%), Pyrexia (n=195, 36.2%), IRR (n=129, 23.9%), Anaemia 111 (20.6%), Fatigue (n=89, 16.5%), Neutropenia 89 (16.5%) and Chills (15.8%).

Severity of Treatment-Related Treatment-Emergent Adverse Events

A total of 322 patients (59.7%) treated with odronextamab monotherapy experienced at least 1 Grade ≥ 3 treatment-related TEAE. By PT, those experienced by ≥5% patients included: Neutropenia (n=73, 13.5%), Anemia (n=54, 10.0%), Neutrophil count decreased (n=43, 8.0%), Lymphocyte count decreased (n=39, 7.2%), CRS (n=34, 6.3%), ALT increased (n=34, 6.3%), AST increased (n=32, 5.9%), and Pneumonia (n=27, 5.0%) (Table 20).

Table 20: Summary of Treatment-Related Treatment-Emergent Adverse Events by System Organ Class/Preferred Term and Severity Grade Experienced by ≥5% of Patients (All Grades Total)

Primary System Organ Class	< 80 mg		80 mg		160 mg		320 mg		Total	
Preferred Term	(N=82)		(N=164)		(N=251)		(N=42)		(N=539)	
	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5
Patients with any Treatment-Related TEAE, n (%)	77 (93.9%)	52 (63.4%)	151 (92.1%)	100 (61.0%)	221 (88.0%)	142 (56.6%)	42 (100%)	28 (66.7%)	491 (91.1%)	322 (59.7%)
Immune system disorders	**43 (52.4%)**	**5 (6.1%)**	**95 (57.9%)**	**8 (4.9%)**	**143 (57.0%)**	**17 (6.8%)**	**28 (66.7%)**	**5 (11.9%)**	**309 (57.3%)**	**35 (6.5%)**
Cytokine release syndrome	42 (51.2%)	5 (6.1%)	93 (56.7%)	8 (4.9%)	139 (55.4%)	17 (6.8%)	27 (64.3%)	4 (9.5%)	301 (55.8%)	34 (6.3%)
General disorders and administration site conditions	**72 (87.8%)**	**4 (4.9%)**	**76 (46.3%)**	**4 (2.4%)**	**109 (43.4%)**	**12 (4.8%)**	**31 (73.8%)**	**4 (9.5%)**	**288 (53.4%)**	**24 (4.5%)**
Pyrexia	63 (76.8%)	1 (1.2%)	41 (25.0%)	1 (0.6%)	68 (27.1%)	3 (1.2%)	23 (54.8%)	1 (2.4%)	195 (36.2%)	6 (1.1%)
Fatigue	19 (23.2%)	2 (2.4%)	25 (15.2%)	1 (0.6%)	35 (13.9%)	4 (1.6%)	10 (23.8%)	0	89 (16.5%)	7 (1.3%)
Chills	45 (54.9%)	1 (1.2%)	9 (5.5%)	0	21 (8.4%)	1 (0.4%)	10 (23.8%)	0	85 (15.8%)	2 (0.4%)
Asthenia	3 (3.7%)	0	9 (5.5%)	2 (1.2%)	15 (6.0%)	3 (1.2%)	6 (14.3%)	2 (4.8%)	33 (6.1%)	7 (1.3%)
Investigations	**48 (58.5%)**	**27 (32.9%)**	**63 (38.4%)**	**41 (25.0%)**	**98 (39.0%)**	**63 (25.1%)**	**16 (38.1%)**	**8 (19.0%)**	**225 (41.7%)**	**139 (25.8%)**
Aspartate aminotransferase increased	13 (15.9%)	3 (3.7%)	22 (13.4%)	12 (7.3%)	30 (12.0%)	14 (5.6%)	6 (14.3%)	3 (7.1%)	71 (13.2%)	32 (5.9%)
Alanine aminotransferase increased	10 (12.2%)	2 (2.4%)	25 (15.2%)	16 (9.8%)	28 (11.2%)	11 (4.4%)	6 (14.3%)	5 (11.9%)	69 (12.8%)	34 (6.3%)
C-reactive protein increased	29 (35.4%)	0	10 (6.1%)	0	18 (7.2%)	1 (0.4%)	2 (4.8%)	1 (2.4%)	59 (10.9%)	2 (0.4%)
Neutrophil count decreased	7 (8.5%)	6 (7.3%)	17 (10.4%)	12 (7.3%)	28 (11.2%)	23 (9.2%)	3 (7.1%)	2 (4.8%)	55 (10.2%)	43 (8.0%)
Lymphocyte count decreased	16 (19.5%)	14 (17.1%)	8 (4.9%)	8 (4.9%)	19 (7.6%)	16 (6.4%)	1 (2.4%)	1 (2.4%)	44 (8.2%)	39 (7.2%)
Platelet count decreased	4 (4.9%)	2 (2.4%)	11 (6.7%)	6 (3.7%)	23 (9.2%)	13 (5.2%)	3 (7.1%)	2 (4.8%)	41 (7.6%)	23 (4.3%)
White blood cell count decreased	8 (9.8%)	2 (2.4%)	8 (4.9%)	4 (2.4%)	19 (7.6%)	10 (4.0%)	2 (4.8%)	1 (2.4%)	37 (6.9%)	17 (3.2%)
Gamma-glutamyltransferase increased	4 (4.9%)	1 (1.2%)	14 (8.5%)	6 (3.7%)	15 (6.0%)	6 (2.4%)	1 (2.4%)	1 (2.4%)	34 (6.3%)	14 (2.6%)

Primary System Organ Class	< 80 mg		80 mg		160 mg		320 mg		Total	
Preferred Term	(N=82)		(N=164)		(N=251)		(N=42)		(N=539)	
	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5
Blood and lymphatic system disorders	**36 (43.9%)**	**25 (30.5%)**	**70 (42.7%)**	**44 (26.8%)**	**87 (34.7%)**	**64 (25.5%)**	**18 (42.9%)**	**10 (23.8%)**	**211 (39.1%)**	**143 (26.5%)**
Anaemia	15 (18.3%)	7 (8.5%)	33 (20.1%)	12 (7.3%)	51 (20.3%)	28 (11.2%)	12 (28.6%)	7 (16.7%)	111 (20.6%)	54 (10.0%)
Neutropenia	9 (11.0%)	8 (9.8%)	40 (24.4%)	31 (18.9%)	33 (13.1%)	28 (11.2%)	7 (16.7%)	6 (14.3%)	89 (16.5%)	73 (13.5%)
Thrombocytopenia	10 (12.2%)	3 (3.7%)	11 (6.7%)	5 (3.0%)	22 (8.8%)	12 (4.8%)	2 (4.8%)	1 (2.4%)	45 (8.3%)	21 (3.9%)
Infections and infestations	**15 (18.3%)**	**5 (6.1%)**	**47 (28.7%)**	**19 (11.6%)**	**65 (25.9%)**	**32 (12.7%)**	**18 (42.9%)**	**12 (28.6%)**	**145 (26.9%)**	**68 (12.6%)**
Pneumonia	3 (3.7%)	3 (3.7%)	10 (6.1%)	7 (4.3%)	19 (7.6%)	12 (4.8%)	5 (11.9%)	5 (11.9%)	37 (6.9%)	27 (5.0%)
Metabolism and nutrition disorders	**23 (28.0%)**	**6 (7.3%)**	**40 (24.4%)**	**9 (5.5%)**	**66 (26.3%)**	**22 (8.8%)**	**15 (35.7%)**	**2 (4.8%)**	**144 (26.7%)**	**39 (7.2%)**
Hypophosphataemia	13 (15.9%)	4 (4.9%)	13 (7.9%)	5 (3.0%)	20 (8.0%)	8 (3.2%)	5 (11.9%)	1 (2.4%)	51 (9.5%)	18 (3.3%)
Decreased appetite	3 (3.7%)	0	14 (8.5%)	0	16 (6.4%)	1 (0.4%)	8 (19.0%)	0	41 (7.6%)	1 (0.2%)
Gastrointestinal disorders	**29 (35.4%)**	**1 (1.2%)**	**41 (25.0%)**	**3 (1.8%)**	**53 (21.1%)**	**9 (3.6%)**	**17 (40.5%)**	**2 (4.8%)**	**140 (26.0%)**	**15 (2.8%)**
Nausea	15 (18.3%)	0	18 (11.0%)	1 (0.6%)	15 (6.0%)	0	4 (9.5%)	0	52 (9.6%)	1 (0.2%)
Diarrhoea	6 (7.3%)	0	14 (8.5%)	0	20 (8.0%)	2 (0.8%)	7 (16.7%)	1 (2.4%)	47 (8.7%)	3 (0.6%)
Vomiting	8 (9.8%)	0	12 (7.3%)	1 (0.6%)	12 (4.8%)	1 (0.4%)	1 (2.4%)	0	33 (6.1%)	2 (0.4%)
Injury, poisoning and procedural complications	**29 (35.4%)**	**4 (4.9%)**	**50 (30.5%)**	**7 (4.3%)**	**45 (17.9%)**	**4 (1.6%)**	**10 (23.8%)**	**1 (2.4%)**	**134 (24.9%)**	**16 (3.0%)**
Infusion related reaction	29 (35.4%)	4 (4.9%)	48 (29.3%)	7 (4.3%)	42 (16.7%)	3 (1.2%)	10 (23.8%)	1 (2.4%)	129 (23.9%)	15 (2.8%)
Nervous system disorders	**18 (22.0%)**	**0**	**42 (25.6%)**	**7 (4.3%)**	**48 (19.1%)**	**9 (3.6%)**	**14 (33.3%)**	**0**	**122 (22.6%)**	**16 (3.0%)**
Headache	11 (13.4%)	0	21 (12.8%)	1 (0.6%)	14 (5.6%)	1 (0.4%)	7 (16.7%)	0	53 (9.8%)	2 (0.4%)
Skin and subcutaneous tissue disorders	**12 (14.6%)**	**0**	**46 (28.0%)**	**1 (0.6%)**	**46 (18.3%)**	**6 (2.4%)**	**18 (42.9%)**	**1 (2.4%)**	**122 (22.6%)**	**8 (1.5%)**
Rash	4 (4.9%)	0	22 (13.4%)	0	12 (4.8%)	2 (0.8%)	9 (21.4%)	0	47 (8.7%)	2 (0.4%)
Pruritus	1 (1.2%)	0	11 (6.7%)	0	10 (4.0%)	0	5 (11.9%)	0	27 (5.0%)	0

Primary System Organ Class	< 80 mg		80 mg		160 mg		320 mg		Total	
Preferred Term	(N=82)		(N=164)		(N=251)		(N=42)		(N=539)	
	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5
Musculoskeletal and connective tissue disorders	**21 (25.6%)**	**1 (1.2%)**	**41 (25.0%)**	**6 (3.7%)**	**33 (13.1%)**	**2 (0.8%)**	**10 (23.8%)**	**0**	**105 (19.5%)**	**9 (1.7%)**
Myalgia	10 (12.2%)	0	17 (10.4%)	0	14 (5.6%)	0	7 (16.7%)	0	48 (8.9%)	0
Arthralgia	4 (4.9%)	0	21 (12.8%)	3 (1.8%)	11 (4.4%)	1 (0.4%)	3 (7.1%)	0	39 (7.2%)	4 (0.7%)
Respiratory, thoracic and mediastinal disorders	**21 (25.6%)**	**6 (7.3%)**	**20 (12.2%)**	**6 (3.7%)**	**40 (15.9%)**	**8 (3.2%)**	**7 (16.7%)**	**1 (2.4%)**	**88 (16.3%)**	**21 (3.9%)**
Cough	5 (6.1%)	0	3 (1.8%)	0	17 (6.8%)	0	2 (4.8%)	0	27 (5.0%)	0
Vascular disorders	**18 (22.0%)**	**4 (4.9%)**	**13 (7.9%)**	**2 (1.2%)**	**33 (13.1%)**	**8 (3.2%)**	**6 (14.3%)**	**0**	**70 (13.0%)**	**14 (2.6%)**
Hypotension	15 (18.3%)	3 (3.7%)	9 (5.5%)	2 (1.2%)	24 (9.6%)	5 (2.0%)	4 (9.5%)	0	52 (9.6%)	10 (1.9%)
Cardiac disorders	**16 (19.5%)**	**2 (2.4%)**	**13 (7.9%)**	**1 (0.6%)**	**27 (10.8%)**	**6 (2.4%)**	**8 (19.0%)**	**1 (2.4%)**	**64 (11.9%)**	**10 (1.9%)**
Tachycardia	11 (13.4%)	2 (2.4%)	5 (3.0%)	0	16 (6.4%)	2 (0.8%)	2 (4.8%)	0	34 (6.3%)	4 (0.7%)

AE, adverse event, CRS, cytokine release syndrome; MedDRA, Medical Dictionary for Regulatory Activities; N, no. of patients; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, system organ class.
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

5.4.5.1. Treatment-Related Treatment-Emergent Adverse Events Leading to Death

A total of 17 (3.2%) patients treated with odronextamab monotherapy experienced treatment-related TEAEs leading to death including Pneumonia (4 [0.7%] patients), and Cardiac arrest (2 [0.4%] patients). Cytomegalovirus infection reactivation, Cytomegaloviral pneumonia, Progressive multifocal leukoencephalopathy, Respiratory syncytial virus bronchitis, Systemic mycosis, Gastric perforation, *Pneumocystis jirovecii* pneumonia, TLS, Toxoplasmosis, death with no further attribution, and CRS were experienced by 1 patient each. In one patient both a fatal Pneumonia and concurrent fatal Pseudomonal sepsis were reported.

5.4.5.2. Serious Treatment-Related Treatment-Emergent Adverse Events

A total of 235 (43.6%) patients experienced at least 1 serious TEAE that was assessed by the investigator as related to odronextamab treatment.

Serious treatment-related TEAEs experienced by ≥3 (0.6%) patients are included in Table 21. The most frequently reported serious treatment-related TEAEs were CRS (n=118, 21.9%), Pneumonia (n=28, 5.2%), Pyrexia (n=22, 4.1%), IRR (n=16, 3.0%), Cytomegalovirus (CMV) infection reactivation, and *Pneumocystis jirovecii* pneumonia (n=7, 1.3% each).

Table 21: Summary of Serious Treatment-Related Treatment-Emergent Adverse Events for Odronextamab Monotherapy during Core Treatment (≥ 3 patients)

	Total (N=539)
Patients with any Treatment-Related Serious TEAE, n (%)	**235 (43.6%)**
Cytokine release syndrome	118 (21.9%)
Pneumonia	28 (5.2%)
Pyrexia	22 (4.1%)
Infusion related reaction	16 (3.0%)
Cytomegalovirus infection reactivation	7 (1.3%)
Pneumocystis jirovecii pneumonia	7 (1.3%)
Encephalopathy	6 (1.1%)
Pneumonitis	6 (1.1%)
Cytomegalovirus infection	5 (0.9%)
Febrile neutropenia	5 (0.9%)
COVID-19	4 (0.7%)
Neurotoxicity	4 (0.7%)
Pulmonary embolism	4 (0.7%)
Tumour lysis syndrome	4 (0.7%)
Cytomegalovirus colitis	3 (0.6%)
Diarrhoea	3 (0.6%)
Herpes zoster	3 (0.6%)
Platelet count decreased	3 (0.6%)
Pneumonia cytomegaloviral	3 (0.6%)
Respiratory tract infection	3 (0.6%)
Somnolence	3 (0.6%)

[a] 1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
[b] 1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
[c] 1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

5.4.6. Adverse Events of Special Interest

Adverse events of special interest (AESI) include CRS and IRR, TLS, central nervous system (CNS) events (identified by potential ICANS events), and infections. The sections below summarize the AESIs for patients treated with odronextamab monotherapy.

5.4.6.1. Cytokine Release Syndrome and Infusion Related Reactions

Among all 539 patients treated, CRS and IRR occurred in 355 (65.9%) patients; 46 (8.5%) patients experienced Grade ≥3 IRR or CRS events. Most events of CRS/IRR were of Grades 1 or 2, with Grade 4 and 5 CRS events reported for 1 patient each in the MCL subtype (Table 22 and Table 23). CRS/IRR events were more frequent in the MCL subtypes, particularly events of Grade 3 and above (See Section 5.4).

Table 24 compare the CRS and IRR events by severity when comparing the 1/20 mg vs 0.7/4/20 mg odronextamab regimens across all patients that received either treatment.

Table 22: Summary of Cytokine Release Syndrome and Infusion Related Reactions with Odronextamab Monotherapy by Cancer Type (All Patients)

	B-NHL (N=524)	ALL (N=1)	CLL/HCL (N=14)	Total (N=539)
Patients with CRS/IRR TEAEs, n (%)	342 (65.3%)	1 (100%)	12 (85.7%)	355 (65.9%)
Severity				
Grade 1 - Mild	157 (30.0%)	1 (100%)	3 (21.4%)	161 (29.9%)
Grade 2 - Moderate	143 (27.3%)	0	5 (35.7%)	148 (27.5%)
Grade 3 - Severe	39 (7.4%)	0	4 (28.6%)	43 (8.0%)
Grade 4 - Life threatening or disabling	2 (0.4%)	0	0	2 (0.4%)
Grade 5 - Death	1 (0.2%)	0	0	1 (0.2%)

ALL, acute lymphoblastic leukemia; B-NHL, B cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; HCL, hairy cell leukemia; IRR, infusion related reaction; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
R1979-HM-1333-Adverse events were coded using MedDRA Dictionary 23.1 and graded using NCI-CTCAE version 4.03.
R1979-ONC-1625-Adverse events were coded using MedDRA Dictionary 24.0 and graded using NCI-CTCAE version 5.0.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0 and graded using NCI-CTCAE version 4.03.
CRS graded per adapted from Lee, 2014 and Lee, 2019.
Data cutoff date: 18 Sep 2022.

Table 23: Summary of Cytokine Release Syndrome and Infusion Related Reactions with Odronextamab Monotherapy by B-NHL Subtype (All B-NHL Patients)

	DLBCL	FL 1-3A	MCL	MZL	Other B-NHL	Total
	(N=276)	(N=171)	(N=26)	(N=25)	(N=26)	(N=524)
Patients with CRS/IRR TEAEs, n (%)	**176 (63.7%)**	**117 (68.4%)**	**23 (88.4%)**	**14 (56%)**	**12 (46.2%)**	**342 (65.3%)**
Severity						
Grade 1 - Mild	90 (32.6%)	52 (30.4%)	8 (30.8%)	4 (16.0%)	3 (11.5%)	157 (30.0%)
Grade 2 - Moderate	71 (25.7%)	54 (31.6%)	7 (26.9%)	6 (24.0%)	5 (19.2%)	143 (27.3%)
Grade 3 - Severe	15 (5.4%)	11 (6.4%)	6 (23.1%)	3 (12.0%)	4 (15.4%)	39 (7.4%)
Grade 4 - Life threatening or disabling	0	0	1 (3.8%)	1 (4.0%)	0	2 (0.4%)
Grade 5 - Death	0	0	1 (3.8%)	0	0	1 (0.2%)

B-NHL, B cell non-Hodgkin lymphoma; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; IRR, infusion related reaction; MCL, mantle cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MZL, marginal zone lymphoma; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
R1979-HM-1333-Adverse events were coded using MedDRA Dictionary 23.1 and graded using NCI-CTCAE version 4.03.
R1979-ONC-1625-Adverse events were coded using MedDRA Dictionary 24.0 and graded using NCI-CTCAE version 5.0.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0 and graded using NCI-CTCAE version 4.03.
CRS graded per adapted from Lee, 2014 and Lee, 2019.
Data cutoff date: 18 Sep 2022.

Table 24: Summary of Cytokine Release Syndrome and Infusion Related Reactions comparing 1/20 mg vs 0.7/4/20 mg Odronextamab regimens (All patients)

Cytokine Release Syndrome and Infusion Related Reactions	1/20mg	0.7/4/20mg	Total
	(N=300)	(N=166)	(N=466)
Severity (total/any grade)			
Grade 1 - Mild	78 (26.0%)	56 (33.7%)	134 (28.8%)
Grade 2 - Moderate	99 (33.0%)	33 (19.9%)	132 (28.3%)
Grade 3 - Severe	30 (10.0%)	5 (3.0%)	35 (7.5%)

Cytokine Release Syndrome and Infusion Related Reactions	1/20mg	0.7/4/20mg	Total
	(N=300)	(N=166)	(N=466)
Grade 4 - Life threatening or disabling	2 (0.7%)	0	2 (0.4%)
Grade 5 - Death	1 (0.3%)	0	1 (0.2%)

R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

Table 25 compares the CRS events (by severity) with the 1/20 mg vs 0.7/4/20 mg odronextamab regimens across all patients while and Table 26 compare the IRR events.

Table 25: Summary of Cytokine Release Syndrome comparing 1/20 mg vs 0.7/4/20 mg Odronextamab regimens (All patients)

Cytokine Release Syndrome	1/20 mg	0.7/4/20 mg	Total
	(N=300)	(N=166)	(N=466)
Severity (total/any grade)			
Grade 1 - Mild	98 (32.7%)	62 (37.3%)	160 (34.3%)
Grade 2 - Moderate	59 (19.7%)	21 (12.7%)	80 (17.2%)
Grade 3 - Severe	23 (7.7%)	3 (1.8%)	26 (5.6%)
Grade 4 - Life threatening or disabling	2 (0.7%)	0	2 (0.4%)
Grade 5 - Death	1 (0.3%)	0	1 (0.2%)

R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

Table 26: Summary of Infusion Related Reactions comparing 1/20 mg vs 0.7/4/20 mg Odronextamab regimens (All patients)

Infusion Related Reaction	1/20	0.7/4/20	Total
	(N=300)	(N=166)	(N=466)
Severity			

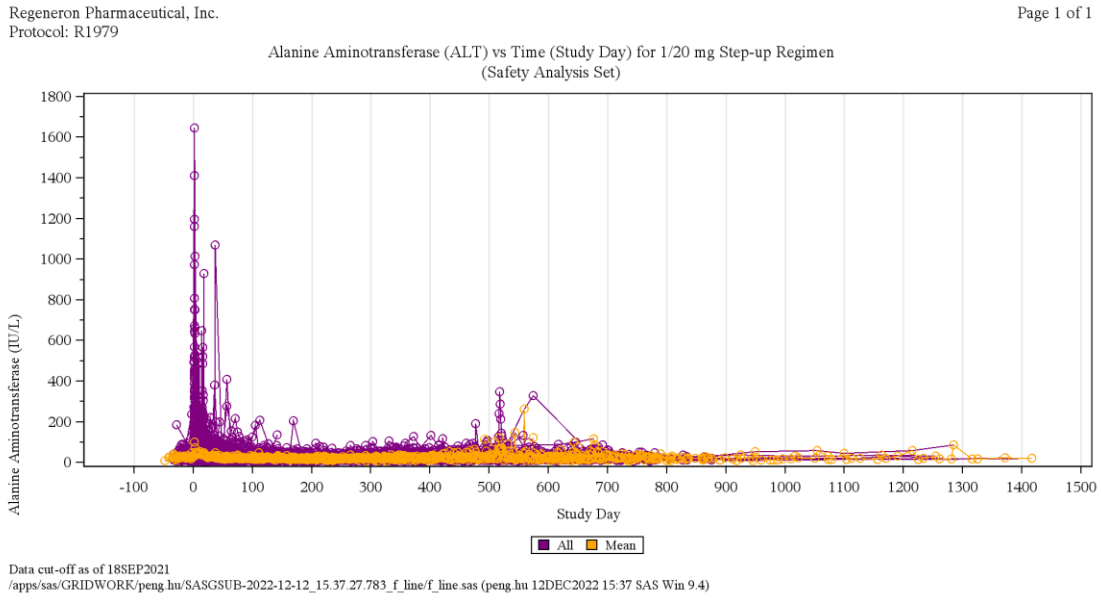
Infusion Related Reaction	1/20	0.7/4/20	Total
	(N=300)	(N=166)	(N=466)
Grade 1 - Mild	18 (6.0%)	8 (4.8%)	26 (5.6%)
Grade 2 - Moderate	56 (18.7%)	16 (9.6%)	72 (15.5%)
Grade 3 - Severe	9 (3.0%)	2 (1.2%)	11 (2.4%)
Grade 4 - Life threatening or disabling	0	0	0
Grade 5 - Death	0	0	0

R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

5.4.6.1.1. Transaminases Elevation (ALT and AST)

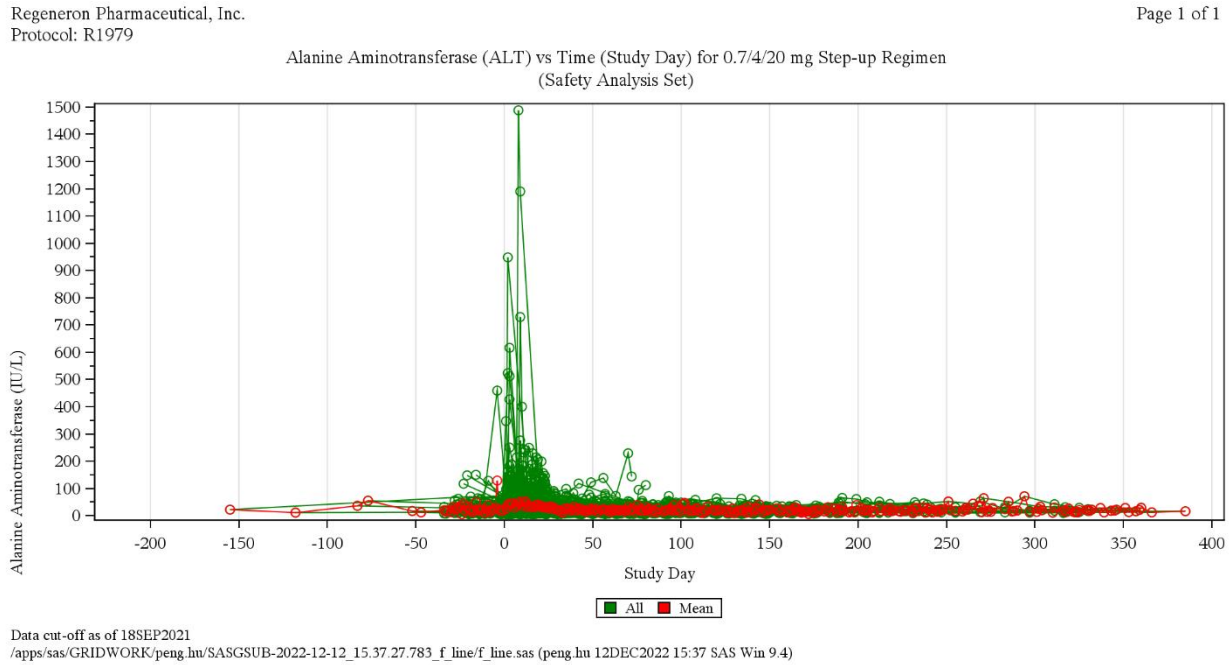
Figure 3, Figure 4 , Figure 5 and Figure 6 show the ALT and AST levels versus the study day for patients receiving odronextamab monotherapy (1/20 mg and 0.7/4/20 mg dosing regimens) in studies R1979-HM-1333 and R1979-ONC-1625. Elevation in liver enzymes were predominantly observed following the initial doses, in most patients resolved spontaneously and did not recur with continued dosing.

Figure 3: Alanine Aminotransferase (ALT) vs. Time (Study Day) for 1/20 mg dosing regimen



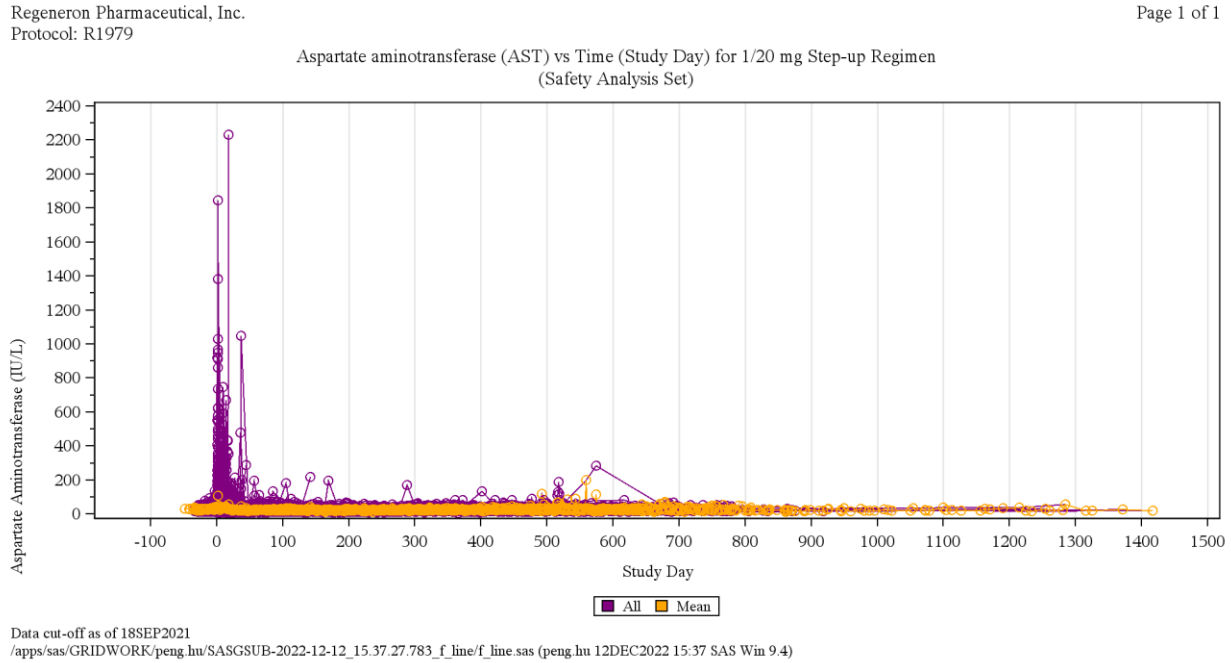
Data cutoff date: 18 Sep 2022

Figure 4: Alanine Aminotransferase (ALT) vs. Time (Study Day) for 0.7/4/20 mg dosing regimen



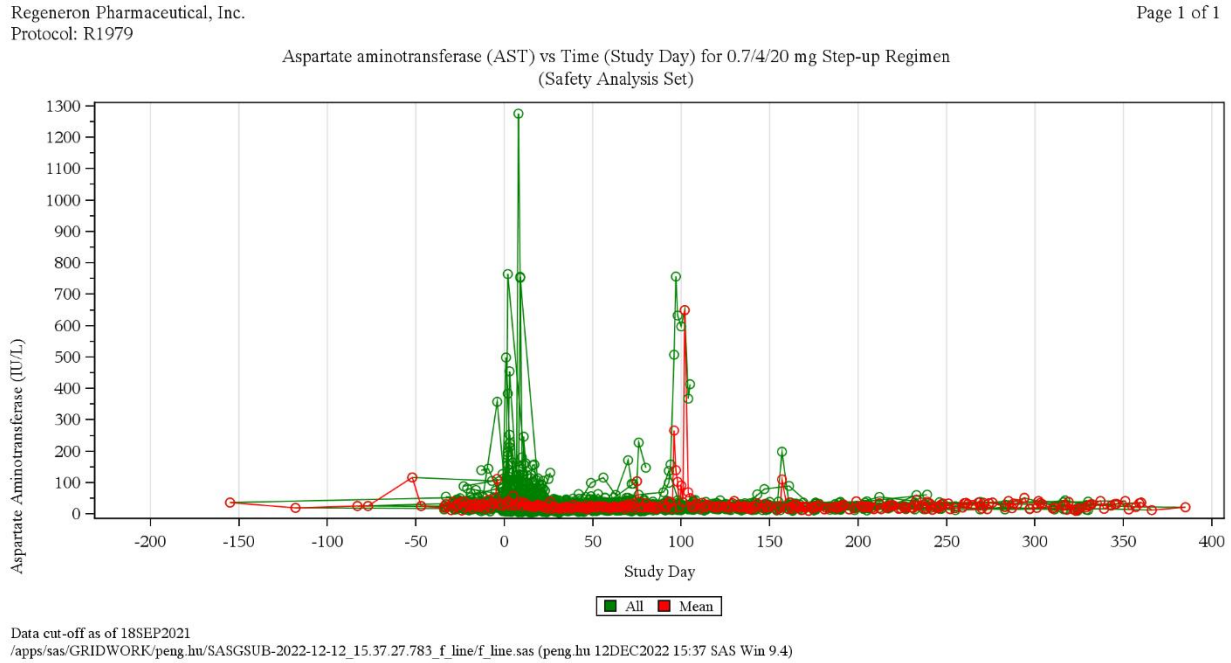
Data cutoff date: 18 Sep 2022

Figure 5: Aspartate Aminotransferase (AST) vs. Time (Study Day) for 1/20 mg Step-up regimen



Data cutoff date: 18 Sep 2022

Figure 6: Aspartate Aminotransferase (AST) vs. Time (Study Day) for 0.7 mg/4 mg/20 mg Step-up regimen



Data cutoff date: 18 Sep 2022

5.4.6.2. Tumor Lysis Syndrome

A total of 8 out of 539 (1.5%) patients treated with odronextamab monotherapy experienced a TEAE of TLS Grade ≥3, including 1 (0.2%) patient with a fatal (Grade 5) event.

For DLBCL patients treated with odronextamab (n=276), 1 (0.4%) patient experienced a TEAE of TLS at the 160 mg dose of odronextamab (Grade 3).

For FL Grades 1-3a patients treated with odronextamab (n=171), 1 (0.6%) patient experienced a TEAE of TLS at the 80 mg dose of odronextamab (Grade 3).

For MCL patients treated with odronextamab (n=26), 3 (11.5%) patients experienced TEAEs of TLS at the 160 mg dose of odronextamab: 2 events were assessed as Grade 3, and 1 event was fatal (Grade 5).

For MZL patients treated with odronextamab (n=25), 1 (4.0%) patient experienced a TEAE of TLS at the 80 mg dose of odronextamab (Grade 3).

No patients with ALL (n=1), or other B-NHL subtypes (n=26) treated with odronextamab experienced an event of TLS.

No patients on the revised (new) regimen have experienced TEAEs of TLS as of the data cutoff date.

5.4.6.3. ICANS Events (neurotoxicity)

The sponsor created a list of MedDRA PTs (Appendix 1) to screen for potential neurotoxicity events with T-effector cells as described by Lee and colleagues (Lee, 2019), ie potential ICANS.

As of the data cutoff date of 18 Sep 2022, potential ICANS events (events of all grades on the Sponsor screening list that were assessed by the investigator as related to odronextamab) were reported in 42 out of 539 (7.8%) patients on the odronextamab monotherapy regimen (Table 27). Eleven (2.0%) patients experienced potential ICANS events that were ≥Grade 3. Among these patients, 2 (0.4%) experienced grade 4 events.

Table 27: Summary of Treatment-Related Sponsor-Identified Potential ICANS Adverse Events by Preferred Term - Odronextamab Monotherapy

Preferred Term	< 80 mg		80 mg		160 mg		320 mg		Total	
	(N=82)		(N=164)		(N=251)		(N=42)		(N=539)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of Patients with any Treatment-Related Sponsor Identified Potential ICANS TEAE, n (%)	4 (4.9%)	0	13 (7.9%)	4 (2.4%)	20 (8.0%)	7 (2.8%)	5 (11.9%)	0	42 (7.8%)	11 (2.0%)
Confusional state	2 (2.4%)	0	4 (2.4%)	1 (0.6%)	5 (2.0%)	0	1 (2.4%)	0	12 (2.2%)	1 (0.2%)
Somnolence	1 (1.2%)	0	2 (1.2%)	1 (0.6%)	5 (2.0%)	0	1 (2.4%)	0	9 (1.7%)	1 (0.2%)
Encephalopathy	0	0	1 (0.6%)	1 (0.6%)	6 (2.4%)	4 (1.6%)	0	0	7 (1.3%)	5 (0.9%)
Mental status changes	0	0	0	0	4 (1.6%)	0	1 (2.4%)	0	5 (0.9%)	0
Neurotoxicity	0	0	2 (1.2%)	1 (0.6%)	2 (0.8%)	1 (0.4%)	1 (2.4%)	0	5 (0.9%)	2 (0.4%)
Aphasia	0	0	1 (0.6%)	0	2 (0.8%)	1 (0.4%)	0	0	3 (0.6%)	1 (0.2%)
Cognitive disorder	0	0	1 (0.6%)	0	1 (0.4%)	1 (0.4%)	0	0	2 (0.4%)	1 (0.2%)
Delirium	1 (1.2%)	0	0	0	1 (0.4%)	1 (0.4%)	0	0	2 (0.4%)	1 (0.2%)
Lethargy	0	0	1 (0.6%)	0	1 (0.4%)	0	0	0	2 (0.4%)	0

Preferred Term	< 80 mg		80 mg		160 mg		320 mg		Total	
	(N=82)		(N=164)		(N=251)		(N=42)		(N=539)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Memory impairment	0	0	1 (0.6%)	0	1 (0.4%)	0	0	0	2 (0.4%)	0
Agitation	0	0	0	0	1 (0.4%)	0	0	0	1 (0.2%)	0
Disorientation	0	0	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Dysarthria	0	0	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Immune effector cell-associated neurotoxicity syndrome	0	0	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0
Monoparesis	0	0	1 (0.6%)	1 (0.6%)	0	0	0	0	1 (0.2%)	1 (0.2%)
Partial seizures	0	0	0	0	0	0	1 (2.4%)	0	1 (0.2%)	0
Seizure	0	0	1 (0.6%)	0	0	0	0	0	1 (0.2%)	0

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.
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

5.4.6.4. Infections

A total of 312 (57.9%) patients treated with odronextamab monotherapy experienced events within the system organ class (SOC) of Infections and infestation, with 153 (28.4%) patients experiencing Grade ≥3 events (Table 28). Pneumonia was the only Grade ≥3 infection experienced by ≥5% of patients (ie, in 44 (8.2%) patients).

Among the 539 patients treated with monotherapy, COVID-19 infections were reported in 52 (9.6%) patients, with 24 (4.5%) patients having Grade ≥3 events. There were 12 (2.3%) deaths reported due to COVID-19-related infections (8 reported as PT COVID-19, 3 as COVID-19 pneumonia, and 1 as SARS-CoV-2 test positive [Section 5.4.4]).

Table 28: Summary of Treatment-Emergent Adverse Events by Infections and Infestations SOC in ≥1% of Patients - Odronextamab Monotherapy

Primary System Organ Class Preferred Term	< 80 mg (N=82)		80 mg (N=164)		160 mg (N=251)		320 mg (N=42)		Total (N=539)	
	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5	All Grades	Grade 3/4/5
Infections and infestations	**39 (47.6%)**	**15 (18.3%)**	**107 (65.2%)**	**51 (31.1%)**	**138 (55.0%)**	**71 (28.3%)**	**28 (66.7%)**	**16 (38.1%)**	**312 (57.9%)**	**153 (28.4%)**
Pneumonia	8 (9.8%)	5 (6.1%)	19 (11.6%)	13 (7.9%)	34 (13.5%)	19 (7.6%)	7 (16.7%)	7 (16.7%)	68 (12.6%)	44 (8.2%)
COVID-19	0	0	25 (15.2%)	8 (4.9%)	24 (9.6%)	15 (6.0%)	3 (7.1%)	1 (2.4%)	52 (9.6%)	24 (4.5%)
Urinary tract infection	8 (9.8%)	0	16 (9.8%)	4 (2.4%)	22 (8.8%)	4 (1.6%)	1 (2.4%)	1 (2.4%)	47 (8.7%)	9 (1.7%)
Upper respiratory tract infection	7 (8.5%)	0	13 (7.9%)	1 (0.6%)	17 (6.8%)	1 (0.4%)	3 (7.1%)	1 (2.4%)	40 (7.4%)	3 (0.6%)
Herpes zoster	1 (1.2%)	0	12 (7.3%)	2 (1.2%)	10 (4.0%)	2 (0.8%)	4 (9.5%)	1 (2.4%)	27 (5.0%)	5 (0.9%)
Oral candidiasis	5 (6.1%)	0	4 (2.4%)	0	8 (3.2%)	0	4 (9.5%)	0	21 (3.9%)	0
Cytomegalovirus infection	0	0	5 (3.0%)	3 (1.8%)	8 (3.2%)	3 (1.2%)	6 (14.3%)	1 (2.4%)	19 (3.5%)	7 (1.3%)
Cytomegalovirus infection reactivation	0	0	7 (4.3%)	4 (2.4%)	8 (3.2%)	3 (1.2%)	3 (7.1%)	1 (2.4%)	18 (3.3%)	8 (1.5%)
Pneumocystis jirovecii pneumonia	3 (3.7%)	1 (1.2%)	3 (1.8%)	2 (1.2%)	11 (4.4%)	8 (3.2%)	0	0	17 (3.2%)	11 (2.0%)
Bronchitis	3 (3.7%)	0	6 (3.7%)	1 (0.6%)	4 (1.6%)	0	2 (4.8%)	0	15 (2.8%)	1 (0.2%)
COVID-19 pneumonia	0	0	10 (6.1%)	9 (5.5%)	4 (1.6%)	3 (1.2%)	1 (2.4%)	1 (2.4%)	15 (2.8%)	13 (2.4%)

Oral herpes	1 (1.2%)	0	10 (6.1%)	1 (0.6%)	4 (1.6%)	0	0	0	15 (2.8%)	1 (0.2%)
Respiratory tract infection	5 (6.1%)	1 (1.2%)	8 (4.9%)	2 (1.2%)	1 (0.4%)	0	0	0	14 (2.6%)	3 (0.6%)
Sinusitis	1 (1.2%)	0	9 (5.5%)	2 (1.2%)	4 (1.6%)	0	0	0	14 (2.6%)	2 (0.4%)
Sepsis	0	0	4 (2.4%)	4 (2.4%)	7 (2.8%)	7 (2.8%)	0	0	11 (2.0%)	11 (2.0%)
Bacteraemia	1 (1.2%)	0	2 (1.2%)	2 (1.2%)	6 (2.4%)	5 (2.0%)	1 (2.4%)	1 (2.4%)	10 (1.9%)	8 (1.5%)
Conjunctivitis	2 (2.4%)	0	3 (1.8%)	0	4 (1.6%)	0	0	0	9 (1.7%)	0
Cytomegalovirus viraemia	0	0	2 (1.2%)	1 (0.6%)	5 (2.0%)	0	2 (4.8%)	1 (2.4%)	9 (1.7%)	2 (0.4%)
Nasopharyngitis	2 (2.4%)	0	1 (0.6%)	0	4 (1.6%)	0	2 (4.8%)	0	9 (1.7%)	0
Herpes simplex	1 (1.2%)	0	3 (1.8%)	0	3 (1.2%)	0	0	0	7 (1.3%)	0
Skin infection	1 (1.2%)	1 (1.2%)	1 (0.6%)	1 (0.6%)	5 (2.0%)	0	0	0	7 (1.3%)	2 (0.4%)
Device related infection	0	0	1 (0.6%)	0	5 (2.0%)	3 (1.2%)	0	0	6 (1.1%)	3 (0.6%)

COVID-19, Coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SOC, system organ class.
R1979-HM-1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
R1979-ONC-1504-Adverse events were coded using MedDRA Dictionary 20.0, and graded using NCI-CTCAE version 4.03
Data cutoff date: 18 Sep 2022.

5.4.6.4.1. Opportunistic Infections

A total of 76 (14.1%) patients treated with odronextamab monotherapy experienced events within the standardized MedDRA query (SMQ) of Opportunistic infections, with 42 (7.8%) patients having Grade ≥3 events (Table 29).

Table 29: Summary of Treatment-Emergent Opportunistic Infections Adverse Events by High Level Term and Severity Grade - Odronextamab Monotherapy

High Level Term, n (%)	< 80 mg		80 mg		160 mg		320 mg		Total	
	(N=82)		(N=164)		(N=251)		(N=42)		(N=539)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grade 3/4/5
Patients with opportunistic Infections TEAE, n (%)	4 (4.9%)	1 (1.2%)	21 (12.8%)	15 (9.1%)	39 (15.5%)	22 (8.8%)	12 (28.6%)	4 (9.5%)	76 (14.1%)	42 (7.8%)
Cytomegalo viral infections	0	0	15 (9.1%)	10 (6.1%)	24 (9.6%)	9 (3.6%)	11 (26.2%)	4 (9.5%)	50 (9.3%)	23 (4.3%)
Pneumocystis infections	3 (3.7%)	1 (1.2%)	3 (1.8%)	2 (1.2%)	13 (5.2%)	9 (3.6%)	1 (2.4%)	0	20 (3.7%)	12 (2.2%)
Herpes viral infections	2 (2.4%)	0	2 (1.2%)	1 (0.6%)	2 (0.8%)	1 (0.4%)	1 (2.4%)	0	7 (1.3%)	2 (0.4%)
Candida infections	0	0	0	0	1 (0.4%)	1 (0.4%)	2 (4.8%)	0	3 (0.6%)	1 (0.2%)
Fungal infections NEC	0	0	1 (0.6%)	1 (0.6%)	1 (0.4%)	0	0	0	2 (0.4%)	1 (0.2%)
Polyomavirus infections	1 (1.2%)	0	1 (0.6%)	1 (0.6%)	0	0	0	0	2 (0.4%)	1 (0.2%)
Aspergillus infections	0	0	0	0	1 (0.4%)	1 (0.4%)	0	0	1 (0.2%)	1 (0.2%)
Lymphoproliferative disorders NEC (excl leukaemias and lymphomas)	0	0	1 (0.6%)	1 (0.6%)	0	0	0	0	1 (0.2%)	1 (0.2%)
Sepsis, bacteraemia, viraemia and fungaemia NEC	0	0	0	0	1 (0.4%)	1 (0.4%)	0	0	1 (0.2%)	1 (0.2%)
Toxoplasma infections	0	0	1 (0.6%)	1 (0.6%)	0	0	0	0	1 (0.2%)	1 (0.2%)
Tuberculous infections	0	0	0	0	1 (0.4%)	1 (0.4%)	0	0	1 (0.2%)	1 (0.2%)

MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
[a] 1333-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 4.03, except for CRS which was graded per Lee et al 2014/2019.

[b] 1625-Adverse events were coded using MedDRA Version 24.1. AE graded using NCI-CTCAE Version 5.0, except for CRS which was graded per Lee et al 2014/2019.
[c] 1504-Adverse events were coded using MedDRA Dictionary 20.0,¬ and graded using NCI-CTCAE version 4.03 .
Data cutoff date: 18 Sep 2022.

5.4.7. Deaths

A total of 111 out of 539 (20.6%) patients treated with odronextamab monotherapy at all DL/regimens died while participating in the study. The primary cause of all deaths reported on treatment and in the post-treatment follow-up period included: progression/recurrence of disease in 62 (11.5%) patients, AEs in 45 (8.3%) patients, and in 4 (0.7%) patients the primary cause of death was reported as 'other' (Table 30).

Details of AEs leading to death are described by preferred term in "Severity of Treatment-Emergent Adverse Events" in Section 5.4.4 and "Severity of Treatment-Related Treatment-Emergent Adverse Events" in Section 5.4.5.

Table 30: Summary of Deaths (by Primary Cause) During Treatment Period for Odronextamab Monotherapy Studies

Deaths (by Primary Cause)	< 80 mg (N=82)	80 mg (N=164)	160 mg (N=251)	320 mg (N=42)	Total (N=539)
Number of Deaths, n (%)	10 (12.2%)	18 (11.0%)	75 (29.9%)	8 (19.0%)	111 (20.6%)
Primary cause of death					
Adverse event	4 (4.9%)	15 (9.1%)	24 (9.6%)	2 (4.8%)	45 (8.3%)
Progression/recurrence of disease	6 (7.3%)	2 (1.2%)	48 (19.1%)	6 (14.3%)	62 (11.5%)
Other	0	1 (0.6%)	3 (1.2%)	0	4 (0.7%)

One death due to disease progression occurred in a patient in R1979-ONC-1504 study monotherapy arm. Data cutoff date: 18 Sep 2022.

5.5. Safety of Combination Studies

5.5.1. Patient Disposition Combination Therapy

The study R1979-ONC-1504 is presently on hold. As of the data cutoff date, 18 Sep 2022, the 32 enrolled patients treated with odronextamab in combination with cemiplimab were off treatment, with 1 patient having completed the per protocol- fixed treatment period. Reasons for discontinuation of treatment were AE (3 [9.4%] patients), death (2 [6.3%]) patients), physician decision (4 [12.5%] patients), clinical progression (5 [15.6%] patients), radiologic progression (16 [50.0%] patients), and subject decision (1 [3.1%] patient).

5.5.2. Treatment Exposure Combination Therapy

A total of 32 patients received odronextamab combination therapy with a median duration of odronextamab exposure of 11.7 weeks (range 1 to 36 weeks), or a median of 10.5 doses administered (range 1 to 22 doses).

5.5.3. Treatment-Emergent Adverse Events

Treatment-emergent adverse events included all AEs (regardless of relationship to odronextamab) that occurred during protocol-defined treatment period and follow-up period. Of the 32 patients treated with odronextamab in combination with cemiplimab, all patients experienced at least 1 TEAE.

Frequency of Treatment-Emergent Adverse Events

The most frequently reported TEAEs in patients (N=32) treated with odronextamab in combination with cemiplimab were, Pyrexia (n=28, 87.5%), CRS (n=24, 75.0%), Anaemia (n=17, 53.1%), Neutropenia (n=13, 40.6% [by composite term]) and Hypotension (n=12, 37.5%).

Severity of Treatment-Emergent Adverse Events

A total of 28 of the 32 (87.5%) patients treated with odronextamab in combination with cemiplimab experienced Grade ≥3 TEAEs.

The most frequently reported Grade ≥3 TEAEs were, Neutropenia (n=12, 37.5%), Anaemia (n=9, 28.1%), Leukopenia (n=8, 25.0% [by composite term]), and Lymphopenia (n=7, 21.9%).

Three (9.4%) patients treated with odronextamab in combination with cemiplimab experienced TEAEs leading to death: Encephalopathy, Intracranial hemorrhage, and Multi-organ dysfunction syndrome and CRS in 1 patient each.

5.5.3.1. Summary of Treatment-Emergent Adverse Events Leading to Discontinuation

Four (12.5%) patients treated with odronextamab in combination with cemiplimab had a total of 6 TEAEs leading to discontinuation (CRS in 2 [6.3%] patient and Encephalopathy, Atrial fibrillation, Dyspnea [secondary to CRS], and Pneumonitis in 1 [3.1%] patient each). Three of these events (CRS, Encephalopathy, and Pneumonitis, each occurring in 1 patient) were Grade 3 or higher.

5.5.3.2. Summary of Serious Treatment-Emergent Adverse Events

Among the 32 patients treated with odronextamab in combination with cemiplimab therapy, 24 (75.0%) patients experienced serious TEAEs (all grades).

The following serious TEAEs were reported in ≥2 patients: CRS (n=14, 43.8%), Pyrexia (n=4, 12.5%), and IRR, urinary tract infection, and pneumonitis (each n=2, 6.3%). Thirteen (40.6%) patients had Grade ≥3 events, with events experienced by ≥2 patients being CRS (n=4, 12.5%) and pneumonitis (n=2, 6.3%).

5.5.4. Summary of Treatment-Related Treatment-Emergent Adverse Events

All patients treated with odronextamab in combination with cemiplimab therapy experienced at least 1 TEAE assessed by the investigator as being related to odronextamab treatment.

Frequency of Treatment-Related Treatment-Emergent Adverse Events

Overall, treatment-related TEAEs reported in ≥25% of patients (all grades) were, pyrexia (n=28, 87.5%), CRS (n=24, 75.0%), ALT increase (n=8, 25%), AST increase (n=8, 25%), CRP increase (n=8, 25%), and hypotension (n=8, 25%).

Severity of Treatment-Related Treatment-Emergent Adverse Events

A total of 26 out of 32 (81.3%) patients treated at any DL with odronextamab in combination with cemiplimab experienced TEAEs assessed as Grade ≥3 and considered related to odronextamab by the investigator. The most frequently reported treatment-related TEAEs of Grade ≥ 3 were, neutropenia (n=10 patients, 31.3%), lymphopenia (n=7, 21.9%), and CRS (n=5, 15.6%).

Two (6.3%) patients treated with odronextamab in combination with cemiplimab therapy experienced a total of 3 TEAEs leading to death: 1 patient had a Grade 5 event of multi-organ failure (secondary to CRS), and 1 patient died of encephalopathy.

5.5.4.1. Serious Treatment-Related Treatment-Emergent Adverse Events

Twenty-two of 32 (68.8%) patients experienced serious TEAEs that were assessed by the investigator as related to odronextamab.

The most frequently reported events, considered serious, related to odronextamab and experienced by ≥2 patients were, CRS (n=14, 43.8%), Pyrexia (n=3, 9.4%), and IRR (n=2, 6.3%).

5.5.5. Adverse Events of Special Interest

Adverse events of special interest (AESI) include CRS and IRR, TLS, CNS toxicities (ICANS), and infections. The sections below summarize the AESIs in patients treated with odronextamab in combination with cemiplimab.

5.5.5.1. Cytokine Release Syndrome and Infusion Related Reactions

Cytokine Release Syndrome (CRS) and IRRs occurred in 28 out of 32 (87.5%) patients treated with odronextamab in combination with cemiplimab. Seven (21.9%) patients experienced TEAEs of CRS/IRR Grade 3 or higher.

5.5.5.2. Tumor Lysis Syndrome

Tumor Lysis Syndrome occurred in 2 out of 32 (6.3%) patients treated with odronextamab in combination with cemiplimab. Both events of TLS were assessed as Grade 3 and determined by the investigator as related to odronextamab.

5.5.5.3. ICANS (Neurotoxicity)

The Sponsor created a list of MedDRA preferred terms (PTs; Appendix 1) to screen for potential neurotoxicity events with T-effector cells as described by (Lee., 2019), ie potential ICANS.

Potential ICANS events on the Sponsor's list that were assessed as related to odronextamab by the investigator, occurred in 6 out of 32 (18.8%) patients treated with odronextamab in combination with cemiplimab. One (3.1%) patient experienced a potential ICANS event of Grade 3 or higher (Encephalopathy).

5.5.5.4. Infections

Sixteen of the 32 (50%) patients treated with odronextamab in combination with cemiplimab experienced events within the SOC of Infections and infestation. The TEAEs within this SOC experienced by these patients included: Oral herpes (n=4, 12.5%), Urinary tract infection (n=3, 9.4%), Viral upper respiratory infection (n=3, 9.4%), and Upper respiratory tract infection (n=2, 6.3%). Four (12.5%) patients experienced Grade ≥3 infections, Urinary tract infection, Clostridium difficile colitis, Infection and Pneumonia each in 1 patient.

5.5.6. Deaths

A total of 7 (21.9%) patients treated with odronextamab in combination with cemiplimab died. The primary cause of all deaths reported on treatment and in the post-treatment follow-up period were disease progression in 4 (12.5%) patients, AEs in 2 (6.3%) patients (Section 5.5.4), and in 1 (3.1%) patient the primary cause of death was reported as 'other'.

5.6. Efficacy

The efficacy data (cutoff date of 15 Sep 2022) for patients with DLBCL and FL grade 1-3a treated with odronextamab monotherapy in the ongoing phase 2 study R1979-ONC-1625 and DLBCL after failure of CAR-T therapy treated in phase 1 study R1979-HM-1333 are presented below and differ from the overall clinical data cutoff for safety (18 Sep 2022). Additional efficacy data for patients treated in study R1979-HM-1333 and study R1979-ONC1625 are published in Bannerji, 2022.

5.6.1. Odronextamab Monotherapy efficacy in Patients with DLBCL 160mg and FL Grade 1-3a 80mg treated in study R1979-ONC-1625

Efficacy data are available for 251 patients with DLBCL or FL grade 1-3a treated in study R1979-ONC-1625 who had received odronextamab monotherapy at a full dose of 160 mg or 80 mg, respectively (either under the original or the modified step-up dosing regimen) and had an opportunity for week-12 tumor assessment in disease-specific cohorts.

As of data cutoff date of 15 Sep 2022, 140 patients with DLBCL were enrolled in study R1979-ONC-1625 and assigned to receive the target dose of 160 mg QW, with 130 patients efficacy evaluable: 67 patients received the 1/20 mg regimen, and 63 patients received the 0.7/4/20 mg regimen. The median duration of study follow-up was 21.29 months (2.6, 29.8). Odronextamab demonstrated clinically meaningful efficacy in patients with DLBCL, including ORR of 49.2% and CR of 30.8% as assessed by Independent Central Review (ICR). The Kaplan Meier estimated median duration of response (CR/PR) is 10.2 months (Table 31).

As of data cutoff date of 15 September 2022, 130 patients with FL Grades 1-3a were enrolled in study R1979-ONC-1625 and assigned to receive the target dose of 80 mg QW, with 121 patients were efficacy evaluable; 68 patients received the 1/20 mg regimen, and 53 patients received the 0.7/4/20 mg regimen. The median duration of study follow-up was 22.37 months (2.6, 33.0). Odronextamab demonstrated clinically meaningful efficacy in patients with FL Grade 1-3a, including ORR of 81.8% and CR of 75.2% as assessed by ICR. The Kaplan-Meier estimated median duration of response (CR/PR) is 20.5 months (Table 31).

For efficacy data based on investigator assessment for the same patients, please see Table 32.

Table 31: Study R1979-ONC-1625: Best Overall Response Based on Independent Central Review per Lugano Classification in Patients with DLBCL and FL Grades 1-3a Treated with Odronextamab monotherapy

	DLBCL 160mg (N=130)	FL Gr. 1-3a 80mg (N=121)
Best Overall Tumor Response Per Lugano		
CR (Complete response)	40 (30.8%)	91 (75.2%)
PR (Partial response)	24 (18.5%)	8 (6.6%)
SD (Stable disease)	5 (3.8%)	7 (5.8%)
PD (Progressive disease)	29 (22.3%)	5 (4.1%)
Missing/UE (Unable to Evaluate)	32 (24.6%)	10 (8.3%)
Response Per Lugano		
Objective Response Rate (CR/ PR)	64 (49.2%)	99 (81.8%)
Disease Control Rate (CR/PR/ SD)	69 (53.1%)	106 (87.6%)
Kaplan-Meier Estimation of Duration of Response (CR/PR) (months)		
Median	10.2	20.5
Duration of Follow-up (months)		
Median	21.29	22.37
Range (Min: Max)	2.6: 29.8	2.6: 33.0

Observed duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) according to IWG Criteria (Cheson, 2014) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed were censored at the last valid tumor measurement.
Data cutoff date: 15 Sep 2022.

Table 32: Study R1979-ONC-1625: Best Overall Response Based on Investigator Assessment per Lugano Classification in Patients with DLBCL and FL grade 1-3a Treated with Odronextamab monotherapy

	DLBCL 160mg (N=130)	FL Gr. 1-3a 80mg (N=121)
Best Overall Tumor Response Per Lugano		
CR (Complete response)	47 (36.2%)	85 (70.2%)
PR (Partial response)	18 (13.8%)	14 (11.6%)
SD (Stable disease)	4 (3.1%)	3 (2.5%)
PD (Progressive disease)	28 (21.5%)	7 (5.8%)
Missing/UE (Unable to Evaluate)	33 (25.4%)	12 (9.9%)
Response Per Lugano		
Objective Response Rate (CR/PR)	65 (50.0%)	99 (81.8%)
Disease Control Rate (CR/PR/SD)	69 (53.1%)	102 (84.3%)
Kaplan-Meier Estimation of Duration of Response (CR/PR) months		
Median	10.2	20.5
Duration of Follow-up (months)		
Median	21.29	22.37
Range	2.6 : 29.8	2.6 : 33.0

Observed duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) according to IWG Criteria (Cheson, 2014) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed were censored at the last valid tumor measurement.
Data cutoff date: 15 Sep 2022.

5.6.2. Odronextamab Monotherapy efficacy in patients with DLBCL 160 mg after failure of prior CAR-T treatment, treated in study R1979-HM-1333

As of data cutoff date of 11 August 2022, 31 patients with DLBCL after failure of CAR-T therapy enrolled in study R1979-HM-1333 and assigned to receive the target dose of 160 mg QW were efficacy evaluable; 20 patients received the 1/20 mg regimen, and 11 patients received the 0.7/4/20 mg regimen. The median duration of study follow-up was 24.25 months (2.7, 38.5). Odronextamab demonstrated clinically meaningful efficacy in patients with DLBCL after failure of CAR-T therapy, including ORR of 48.8% and CR of 32.3% as assessed by ICR. The Kaplan-Meier estimated median duration of response (CR/PR) is not reached (NR). These data based on ICR and investigator assessment are presented in Table 33.

Table 33: Study R1979-HM-1333: Best Overall Response Derived Based on Independent Central Review and Investigator Assessment per Lugano Classification in Patients with DLBCL after CART-T failure Treated with Odronextamab monotherapy

DLBCL 160mg Post CAR-T failure	Independent Central Reviewers (N=31)	Investigator Assessment (N=31)
Best Overall Tumor Response Per Lugano		
CR (Complete response)	10 (32.3%)	10 (32.2%)
PR (Partial response)	5 (16.1%)	2 (6.5%)
SD (Stable disease)	2 (6.5%)	1 (3.2%)
PD (Progressive disease)	3 (9.7%)	9 (29.0%)
Missing/UE (Unable to Evaluate)	11 (35.5%)	9 (29.0%)
Response Per Lugano		
Objective Response (CR/PR)	15 (48.8%)	12 (38.7%)
Disease Control (CR/PR/SD)	17 (54.8%)	13 (41.9%)
Kaplan-Meier Estimation of Duration of Response (CR/PR) months		
Median	Not Reached	Not Reached
Duration of Follow-up (months)		
Median	24.25	24.25
Range	2.7: 38.5	2.7: 38.5

Observed duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) according to IWG Criteria (Cheson, 2014) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed were censored at the last valid tumor measurement.
Data cutoff date: 11 Aug 2022.

6. GUIDANCE FOR THE INVESTIGATORS

6.1. Important Identified and Potential Risks

An identified risk refers to an untoward occurrence for which there is adequate evidence of association with the medicinal product of interest. A potential risk refers to an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest, but where an association has not been confirmed. The important identified and potential risks for odronextamab have been determined based on observation in preclinical toxicology or clinical studies with odronextamab; risks reported with T cell engaging immunotherapies; as well as risks generally associated with mAbs.

Important Identified Risks:

- Cytokine release syndrome and IRRs
- Tumor lysis syndrome
- Infections (including Hepatitis B and Progressive multifocal leukoencephalopathy)

Important Potential Risks:

- Central Nervous System Adverse Events (ICANS)
- Systemic hypersensitivity reactions
- Clinical consequences of immunogenicity (anti-odronextamab antibody formation)
- Embryo-fetal toxicity

6.2. Important Identified Risks

6.2.1. Cytokine Release Syndrome and Infusion Related Reactions

Cytokine release syndrome and IRRs are important identified risks of treatment with odronextamab. The MOA of any T cell engaging immunotherapy, such as odronextamab, is non-physiologic T cell activation with cytokine release. The incidence and severity of CRS might be related to both tumor type and tumor burden.

There is significant overlap in the clinical presentation of CRS and IRR, both of which may include fever, rigors, tachycardia, hypotension, hypoxia, and bronchospasm. The symptomatology associated with both entities is consistent with an underlying mechanism of exaggerated immune response and release of inflammatory cytokines.

Odronextamab Monotherapy Studies:

In the ongoing studies with odronextamab monotherapy of the 539 patients treated, 166 patients have been treated with the revised step-up regimen (0.7/4/20 mg):

- A total of 303/539 (56.2%) patients experienced CRS events, with 34 (6.3%) patients experiencing Grade 3 or higher CRS events
  - Of the 166 patients treated with the revised step-up regimen (0.7/4/20 mg) a total of 86 (51.8%) patients experienced CRS events. Of the 86 (51.8%) patients, the highest grade of CRS reported was Grade 3 in 3 patients (1.8%), Grade 2 in 21 patients (12.7%), and Grade 1 in 62 (37.3%) patients. No Grade 4 or 5 CRS events were reported and 1 (0.6%) patient on the revised regimen discontinued treatment due to CRS.
- A total of 135/539 (25.0%) patients experienced IRR events, with 15 (2.8%) patients experiencing Grade 3 or higher IRR events
  - Of the 166 patients treated with the revised step-up regimen, a total of 26 (15.7%) patients treated experienced IRR events. Of the 26 (15.7%) patients the highest grade of IRR reported was Grade 3 in 2 patients (1.2%), Grade 2 in 16 patients

(9.6%), and Grade 1 in 8 patients (4.8%). No Grade 4 or 5 IRR events were reported and 1 (0.6%) patient on the revised regimen discontinued treatment due to IRR

The revised step-up dosing regimen which was implemented to improve the tolerability was successful in reducing the incidence and severity of CRS events. Incidence of any grade CRS events decreased from 183 of 300 (61%) patients with the 1/20 mg regimen to 86 of 166 (51.8%) patients with the revised regimen and grade 3 or higher CRS events decreased from 26 (8.7%) with the 1/20 regimen to 3 (1.8%) with the revised regimen. In addition, the overall incidence of grade 2 or higher CRS events decreased from 85 (28.3%) with the 1/20 regimen to 24 (14.5%) with the revised regimen Table 25.

Overall, CRS or IRR events predominantly occurred during the step-up dosing period of study treatment and typically transient, even when higher doses of odronextamab were administered in subsequent weeks. Cytokine release syndrome/IRR events were manageable with antipyretics, antihistamines, tocilizumab and/or corticosteroid therapy, and supportive care.

In Combination with Cemiplimab:

In study R1979-ONC-1504, 32 patients were treated with odronextamab in combination with cemiplimab. Of the 32 patients, 28 (87.5%) patients experienced CRS/IRR events, with 7 (21.9%) patients experiencing grade 3 or higher events. The highest grade of CRS/IRR was grade 3 in 6 (18.8%) patients and Grade 5 (fatal event) in 1 (3.1%) patient. Two patients discontinued treatment due to CRS.

Risk Mitigation and Monitoring Plan

Risk monitoring and management rely upon close follow-up of patients during and after infusions with availability of appropriate personnel, emergency equipment, and medication (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, anti- IL-6 therapy such as tocilizumab and/or epinephrine) to manage any events.

Odronextamab study protocols include extensive clinical and laboratory monitoring plans for early detection, monitoring, treatment, and prophylaxis of CRS/IRR events. Please refer to study protocols for details. Some of the measures include:

- Monitoring during and after odronextamab administration (see protocol for details).
- Split dosing: Initial and intermediate IV doses of odronextamab to be administered as 2 separate infusions, each over 4 hours on 2 consecutive days.
- Premedication with dexamethasone, antihistamines and/or antipyretics from week 1 through to the first full weekly dose administered as a single infusion.
- Guidance on interruption, termination, grading, and management of IRR/CRS including recommendations for anti-IL6 medication (eg tocilizumab) and corticosteroids are included in the study protocols.
- Delayed introduction of the second T-cell activation signal from an anti-PD-1 antibody or CD22 x CD28 bispecific antibody when used in combination with odronextamab (please see the specific protocols for details)
- The following events should be reported as an AESI (see individual protocols for a complete list) within 24 hours of identification:

- Grade 2 or greater CRS.
- Grade 3 or greater IRR.

6.2.2. Tumor Lysis Syndrome

Tumor lysis syndrome is considered to be an important identified risk of treatment with odronextamab. Tumor lysis syndrome is an oncologic emergency that may occur in patients with lymphoproliferative malignancies with high tumor burden and high proliferative index. Tumor lysis syndrome can develop spontaneously or following initiation of cytotoxic therapies due to the release of intracellular contents from lysed malignant cells. Clinically active therapies such as odronextamab have the potential to precipitate events of TLS.

Patients considered most at risk for TLS include those with a leukemic component with a high circulating lymphocyte/lymphoblast count and aggressive B-NHL with a high tumor burden (including bone marrow and extra medullary organ involvement).

Odronextamab Monotherapy Studies:

In the ongoing studies with odronextamab monotherapy (at any dose), of the 539 patients treated, a total of 8 (1.5%) patients experienced TLS events; all events were Grade ≥3. Events of TLS were assessed as related to odronextamab by the investigators in 7 (1.3%) patients. The highest grade reported was Grade 3 in 6 (1.1%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%). Two (0.4%) patients discontinued treatment because of TLS events.

In Combination with Cemiplimab:

In study R1979-ONC-1504, 2 (6.3%) patients experienced TLS events. All events were assessed as Grade 3 and related to odronextamab. No patients discontinued the study due to TLS.

Risk Mitigation and Monitoring Plan

- Risk minimization focuses on exclusion from study patients with known hypersensitivity to both allopurinol and rasburicase.
- Odronextamab study protocols include extensive clinical and laboratory monitoring plans for early detection, monitoring, treatment, and prophylaxis, as described below
- The following events should be reported as AESI (see individual protocols for a complete list) within 24 hours of identification:
  - Grade 3 or higher TLS

Recommendations for Tumor Lysis Syndrome Prophylaxis

All patients should have adequate fluid intake (approximately 2 to 3 L/day) orally or IV (if unable to take oral fluids) starting 1 to 2 days prior to the odronextamab infusion and continued for at least 24 hours after end of infusion until the patient tolerates the QW dose of odronextamab administered as a single infusion, through week 4 of study treatment, or until the investigator determines that the patient is not at risk for TLS, whichever is later.

Patients considered to be at risk for TLS (for example, patients with CLL, aggressive B-NHL classified as intermediate or high risk (as described in Table 34 below) should have the following additional measures taken for TLS prophylaxis:

- Such patients should receive prophylaxis with allopurinol (or other hypouricemic agent). Allopurinol should begin preferably 7 to 10 days prior to the first infusion of study drug, but not less than 48 hours prior to the first administration. Patients who cannot tolerate allopurinol or other hypouricemic agent and who are at risk for TLS should be monitored closely and treated with rasburicase according to the prescribing information and pertinent institutional guidelines for TLS prophylaxis.
- In addition to oral hydration noted above, IV hydration (approximately 1.5 to 2 L) should be administered as permitted by the patient's hemodynamic status and according to the investigator's clinical judgment.
- If laboratory abnormalities that in the investigator's judgment indicate ongoing TLS are observed in this baseline laboratory assessment, the first dose of study treatment must be delayed until resolution of laboratory abnormalities. If needed, the patient should receive an extended period of TLS prophylaxis prior to the initiation of odronextamab dosing.
- Patients should continue oral hypouricemic agent (if feasible) or rasburicase until the patient tolerates the QW dose of odronextamab administered as a single infusion, through week 4 of study treatment, or until the investigator determines that the patient is not at risk for TLS, whichever is later.

Recommended Monitoring for Tumor Lysis Syndrome

The TLS risk should be assessed by the investigator before each study drug administration (including an assessment prior to each split infusion, if applicable) until the patient has been determined to tolerate the QW dose of odronextamab administered as a single infusion, through week 4 of study treatment, or until the investigator determines that the patient is not at risk for TLS, whichever is later.

Table 34: Tumor Lysis Syndrome Risk Classification and Monitoring for aggressive lymphomas

Risk Classification	Criteria (any one of the below)	Recommended Monitoring
Low Risk	• All measurable lymph nodes with largest diameter <5 cm by radiologic assessment • An absolute lymphocyte counts <25 × 10^9/L. • LDH <2 x ULN	Should be monitored according to standard clinical practice or local institutional guidelines.
Intermediate Risk	• Any measurable lymph node with largest diameter ≥5 cm and <10 cm by radiologic assessment • An absolute lymphocyte count ≥25 × 10^9/L • LDH ≥2 x ULN	Evaluations for TLS should be performed prior to study treatment administration and approximately 8 and 24 hours following the start of study treatment administration.

High Risk	• The presence of any lymph node with the largest diameter ≥10 cm by radiologic assessment • The presence of an absolute lymphocyte count ≥25 × 10^9/L AND a measurable lymph node with the largest diameter ≥5 cm by radiologic assessment • Patients with intermediate risk AND Renal dysfunction (creatinine clearance <80 mL/min OR uric acid, potassium and/or phosphate >ULN) • Bone marrow infiltration ≥5% • Splenomegaly due to lymphoma	Evaluations for TLS should be performed prior to study drug administration and approximately 4, 8, 12 and 24 hours following the start of study treatment administration.

Laboratory investigations for TLS pre-dose and at approximately 4, 8, 12, and 24 hours following the start of study drug administration, as discussed in Table 34 and below in Table 35, should include serum calcium, potassium, phosphate, uric acid, LDH, and creatinine. Laboratory samples should be sent for immediate analysis, and the results must be reviewed promptly by the investigator. It is important to ensure that a nephrology consultation, emergency dialysis, and telemetry are available if needed to manage TLS.

If any laboratory or clinical abnormality indicative of TLS in the investigator's clinical judgment is observed in the pre-dose laboratory assessment (including prior to each split infusion if applicable), the study treatment must be delayed until resolution. Pre-dose laboratory results must be reviewed prior to administration of odronextamab.

Patients who are at risk for TLS as assessed by the investigator must be closely monitored during and at least 24 hours following study drug administration in an appropriate facility. If hospitalized, 24-hour laboratory results must be reviewed before the patient is discharged. If there is evidence of ongoing TLS, additional laboratory assessments and close monitoring should be considered beyond 24 hours following the study drug administration.

Table 35: Diagnosis of Laboratory and Clinical Tumor Lysis Syndrome*

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/L)	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/L)	
Hyperkalemia	Potassium >6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesia, muscle twitching, carpopedal spasm, Trousseau's sign,

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
	(1.75 mmol/L) or ionized calcium <4.5 mg/dL (1.12 mmol/L)†	Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury ‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value >1.5 times the upper limit of the age appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/h for 6 hours

* In laboratory tumor lysis syndrome, ≥2 metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death. The laboratory abnormalities or clinical abnormalities should be suggestive of TLS in the opinion of the investigator.
† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 x (4 – albumin in grams per deciliter).
‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting ≥6 hours. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome (Howard, 2011).

Dose Modification of Odronextamab for Patients who Experience Tumor Lysis Syndrome

If a patient receiving study treatment develops ≥1 laboratory or clinical abnormalities that are judged by the investigator to indicate TLS, study drug administration must be suspended immediately until all laboratory abnormalities and clinical signs/symptoms of TLS have resolved (Table 36). Thus, if the patient is receiving a split dose, laboratory evaluation for TLS must be done after the first half-dose, and the second half-dose must not be administered during the current cycle if there are any signs of TLS.

Table 36: Management Guidance and Study Drug Dosing in Setting of Tumor Lysis Syndrome

Study Drug Administration	Outcome of TLS[1]	Action with odronextamab	Rechallenge[2]	TLS Management Guidance
TLS occurs with Initial dose	Any grade of TLS that does not resolve	Permanently discontinue	Not applicable	
	Any Grade of TLS that resolves	Temporary pause	Upon resolution of TLS, resume treatment with only first half of the initial dose (0.2 mg) and monitor for TLS. If no recurrence of TLS, then increase next dose to 0.7 mg administered as split doses (0.2/0.5 mg) **at least 2 days** apart but not more than 3 days apart. If no recurrence of TLS, dose may be escalated to a split intermediate dose at least 2 days apart but not more than 3 days apart.	

Study Drug Administration	Outcome of TLS[1]	Action with odronextamab	Rechallenge[2]	TLS Management Guidance
			If no recurrence of TLS with intermediate dose, escalate to next higher dose specified in protocol as split dose **at least 2 days** apart but not more than 3 days apart.	• A patient who has laboratory or clinical abnormalities indicative of TLS should be hospitalized for monitoring. • IV fluids should be initiated (approximately 150 to 200 mL/h). • A rapidly rising serum potassium level is a medical emergency and should be managed according to standard clinical practice or local institutional guidelines. Other electrolyte abnormalities including hypocalcemia, hyperphosphatemia and hyperuricemia should be managed according to standard clinical practice or local institutional guidelines. • Monitor for symptoms or signs of TLS. If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine with an expedited assessment. • Once the diagnosis of TLS is determined, intensive monitoring and multi-disciplinary management will be according to standard clinical practice or local institutional guidelines. Strongly recommend consultation with the nephrology service to ensure that emergency dialysis is available. Ensure that telemetry is available for monitoring.
TLS occurs with Intermediate and/or subsequent doses	Any Grade of TLS that does not resolve	Permanently discontinue	Not applicable	
	Any Grade of TLS that resolves	Temporary pause	Upon resolution of TLS, reduce previously received dose by 50% and monitor for TLS. If no recurrence of TLS, then escalate to the dose where TLS was last noted. This dose needs to be administered as a split dose **at least 2 days** apart but not more than 3 days apart. If no recurrence of TLS, dose may escalate to next higher dose specified in protocol as split dose **at least 2 days** apart but not more than 3 days apart.	

[1] Resolution of TLS is defined as no clinical or laboratory abnormalities suggestive of TLS in the investigator's judgment.
[2]If 2 consecutive TLS events occur, discuss the plan of study treatment with the study's Regeneron medical monitor. The goal is to idle the patient at a dose just below that which produces TLS until there is sufficient debulking of the tumor to allow dose escalation.

6.2.3. Serious Infections

Serious Infections are considered an important identified risk. Based on the MOA, treatment with odronextamab may result in pronounced B cell depletion and hypogammaglobulinemia. Marked depletion of B cells can increase the risk of severe infections, including risk of hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML).

Odronextamab Monotherapy Studies:

Of the 539 patients treated with odronextamab monotherapy, a total of 312 (57.9%) patients experienced events within the SOC of Infections and infestation; in 153 (28.4%) patients, events were grade 3 or higher.

Frequently reported events within the SOC of Infections and infestations included Pneumonia in 68 (12.6%) patients, COVID-19 in 52 (9.6%) patients, urinary tract infection in 47 (8.7%) patients, upper respiratory tract infection in 40 (7.4%) patients, Herpes zoster in 27 (5.0%) patients, and oral candidiasis in 21 (3.9%) patients. The most frequently reported grade 3 or higher events were pneumonia in 44 (8.2%) patients, COVID-19 in 24 (4.5%) patients, *Pneumocystis jirovecii* pneumonia in 11 (2.0%) patients, urinary tract infection in 9 (1.7%) patients, CMV infection reactivation in 8 (1.5%) patients, CMV infection in 7 (1.3%) patients, Herpes zoster in 5 (0.9%) patients, and Upper respiratory tract infection in 3 (0.6%) patients (Table 28).

Twenty-four (4.5%) patients discontinued treatment due to infections; pneumonia in 6 (1.1%) patients; COVID-19 pneumonia in 3 (0.6%) patients, COVID-19, CMV infection reactivation, *Pneumocystis jirovecii* pneumonia (PJP) in 2 (0.4%) patients each, abscess neck, bronchitis viral, CMV infection, device related infection, meningitis, osteomyelitis, PML, pulmonary tuberculosis, sepsis, septic shock, and toxoplasmosis in 1 (0.2%) patient each. Infections with a fatal outcome were reported in 29 (5.4%) patients, with 18 patients' events assessed as related to odronextamab by the investigators; pneumonia in 4 patients; CMV infection reactivation, PJP pneumonia, pneumonia cytomegaloviral, PML, pseudomonal sepsis, respiratory syncytial virus bronchitis, systemic mycosis, and toxoplasmosis in 1 patient each. Fatal events assessed as not related to odronextamab included COVID-19 in 8 patients, sepsis in 4 patients, pneumonia and COVID-19 pneumonia in 3 patients each (section 5.3.4.) and 1 patient with event of *Escherichia Coli* sepsis.

Hepatitis B reactivation and PML:

In patients treated with odronextamab monotherapy, 1 (0.2%) patient experienced hepatitis B reactivation and a fatal event of PML was reported in 1 (0.2%) patient.

Further information on reported infections, including opportunistic infections, is included in Section 5.4.6.4.

In combination with cemiplimab:

In study R1979-ONC-1504, 16 patients (50.0%) experienced events of infection, including 5 (15.6%) patients with infections assessed by the investigator as related to odronextamab. The highest severity of infections was grade 3; there were no grade 4 or grade 5 events. Two patients experienced infections that were assessed by investigator as serious and related to odronextamab (Infection and Urinary tract infection), the outcome of both events was reported as resolved.

Hepatitis B reactivation and PML:

No events of hepatitis B reactivation or PML have been reported in the patients treated with odronextamab in combination with cemiplimab.

Risk Minimization, Monitoring and Management Plan

- Risk minimization focuses on exclusion from study of candidates with known active infections and episode of infection requiring hospitalization or treatment with IV antibiotics prior to first administration of odronextamab including uncontrolled hepatitis B. (See individual protocols for details)
- Protocols include guidance on monitoring IgG levels including at baseline as well as periodic monitoring throughout the study and recommendation on supplementation
  - ie, in patients with severe hypogammaglobulinaemia (<400 mg/dL) or in patients with recurrent episodes of infection with immunoglobulin levels between 400 to 600 mg/dL, supplementation with IV immunoglobulin (IVIG) should be considered in accordance with the local institutional guidelines.
- Protocols include guidance on infections prophylaxis. Standard measures of prophylaxis for PJP and antivirals for patients with prior herpes simplex virus (HSV) or CMV infections should be considered in accordance with the local institutional standards, as well as National Comprehensive Cancer Network (National Comprehensive Cancer Network [NCCN], 2019), American Society of Clinical Oncology (ASCO) (Taplitz, 2018), or European Society for Medical Oncology (ESMO) (Klastersky, 2016) guidelines.
- Concomitant live-attenuated vaccines use is prohibited (see protocol for details)
- The following events should be reported as AESI (see individual protocols for a complete list) within 24 hours of identification
  - Grade 3 or greater infections
  - Hepatitis B reactivation
  - CMV infection

6.3. Important Potential Risks

6.3.1. ICANS (Central Nervous System Adverse Events)

Central nervous system symptoms such as confusion, delirium, and aphasia have been observed with CAR-T therapy and previously considered to be part of CRS (Lee, 2014). These symptoms are now considered to be a separate syndrome (ICANS) although cytokines may be implicated in the pathophysiology (Lee, 2019).

The sponsor created a list of MedDRA PTs (Appendix 1) to screen for potential neurologic events with T effector cells as described by (Lee, 2019).

Odronextamab monotherapy studies:

In the 2 ongoing studies with odronextamab monotherapy, a total of 42 (7.8%) patients were identified with events within the sponsor list of potential ICANS terms that were assessed by the investigator as related to odronextamab. Frequently reported potential ICANS events were confusional state in 12 (2.2%) patients, somnolence in 9 (1.7%) patients, encephalopathy in 7 (1.3%) patients, mental status changes and neurotoxicity in 5 (0.9%) patients each, and aphasia in 3 (0.6%) patients.

In 11 (2.0 %) patients, events within the sponsor list of potential ICANS terms that were assessed by the investigator as related to odronextamab were Grade ≥3 (Table 27); two life-threatening events were reported. No fatal potential ICANS were reported. Five (0.9%) patients discontinued treatment due to potential ICANS events: Grade 2 Encephalopathy in 3 (0.6%) patients, and Grade 3 Neurotoxicity and Grade 2 Aphasia in 1 (0.2%) patient each.

In combination with cemiplimab:

In study R1979-ONC-1504, 6 (18.8%) patients experienced events within the sponsor list of potential ICANS terms that were assessed by the investigator as related to odronextamab; Ataxia was reported in 2 (6.3%) patients; all other events were reported in 1 patient each (Confusional state, Disorientation, Disturbance in attention, Encephalopathy, Somnolence, and Tonic convulsion). Treatment-related potential ICANS events with fatal outcome included Encephalopathy in 1 (3.1%) patient.

Risk Minimization, Monitoring and Management Plan

- Patients with known CNS pathology are excluded from the studies
- Protocol includes guidance on monitoring, management, and study drug modifications
- The following events should be reported as an AESI (see protocol for a complete list) within 24 hours of identification:
  - Grade ≥2 CNS adverse events (ICANS events)

6.3.2. Systemic Hypersensitivity Reactions

As with protein therapeutics, acute allergy/hypersensitivity reactions may develop immediately or within a few hours of infusion.

The events of systemic hypersensitivity were selected using SMQ of hypersensitivity (narrow), excluding event of IRR, that were assessed by the investigator as related to odronextamab (events of IRR are discussed in Section 6.2.1.

Odronextamab monotherapy studies

In the ongoing studies with odronextamab monotherapy, among the 539 patients treated, a total of 79 (14.7%) patients experienced events within the narrow SMQ of Hypersensitivity that were assessed by the investigator as related to odronextamab (excluding IRR events discussed in Section 6.2.1); among these, 6 (1.1%) patients experienced Grade 3 events (there were no Grade 4 or Grade 5 hypersensitivity events reported). Most frequently reported odronextamab-related

TEAEs were Rash in 47 (8.7%) patients, Rash erythematous in 8 (1.5%) patients, and Rash maculo-papular in 7 (1.3%) patients.

In combination with cemiplimab:

In R1979-ONC-1504, 3 (9.4%) patients experienced events within the narrow SMQ of hypersensitivity that were assessed by the investigator as related to odronextamab (excluding IRR events discussed in Section 6.2.1). Events included rash and rash pruritic; all were Grade 1. No Grade 3 or higher events were reported.

Risk Mitigation and Monitoring Plan

- Risk minimization focuses on exclusion of patients with history of allergic reactions attributed to compounds of similar chemical or biologic composition of odronextamab.
- Emergency equipment and medication for the treatment of acute infusion reactions (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use.
- Guidance on monitoring, interruption, termination, grading, and management of systemic hypersensitivity are included in the protocol.
- The following events should be reported as AESI (see individual protocols for a complete list) within 24 hours of identification
  - Grade 3 or greater allergic reaction

6.3.3. Clinical Consequences of Immunogenicity (Anti-Odronextamab Antibody Formation)

As with all therapeutic proteins, there is a potential for immunogenicity after administration of monoclonal antibodies.

In study R1979-HM-1333, based on the available data from 133 patients, 1 patient had treatment-emergent ADA with low titer during the safety follow-up period (Section 5.2.1).

In study R1979-ONC-1625, based on the available data from 173 patients, 5 patients had treatment-emergent ADA (Section 5.2.2).

In study R1979-ONC-1504, no patients have tested positive for anti-odronextamab antibodies on the study (Section 5.2.3).

Risk Characterization and Monitoring Plan

Anti-odronextamab antibody status will be assessed as described in the protocol.

6.3.4. Embryo-Fetal Toxicity

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of odronextamab on reproductive organs in males and females are unknown.

Published data on B cell-deficient mice and B cell-modulating drugs have shown no adverse effects on fetal development per se; B cell-depletion in neonates may cause immunosuppression (RITUXAN® USPI, 2018) (BLINCYTO® USPI, 2017) (GAZYVA® USPI, 2016).

As of the data cutoff date, there were no reports of use of odronextamab during pregnancy or breastfeeding.

Risk Mitigation and Monitoring Plan

Exclusion criteria include:

Women of childbearing potential* or men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Sperm donation is prohibited during the study and for 6 months after the last dose of the assigned study treatment. Highly effective contraceptive measures include:

a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated ≥2 menstrual cycles prior to screening
b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
c. bilateral tubal ligation/occlusion
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the study patient and that the partner has obtained medical assessment of surgical success for the procedure).
e. sexual abstinence[†], [‡].

* Women of childbearing potential are defined as women who are fertile following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a post-menopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance.

Pregnancy testing and contraception are not required for women with documented hysterectomy.

[†]Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

[‡]Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

If a woman were to become pregnant while taking odronextamab, treatment with odronextamab should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

Any pregnancy occurring in a female patient or female partner of a male patient must be reported to sponsor (see protocol for details).

6.4. Potential for Drug Interaction

No formal drug-drug interaction studies have been conducted. Transient release of cytokines has been observed predominantly during initial weeks of dosing. Cytokines may suppress CYP450 enzymes (Morgan, 2001). For patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) is recommended especially during the initial weeks of therapy.

6.5. Treatment of Overdose

Patients who are overdosed will be treated symptomatically. Currently, there is no known antidote for odronextamab. Occurrence of overdose must be reported to sponsor (or designee) within 24 hours (see individual protocols for details).

6.6. Reference Safety Information

The Reference Safety Information (RSI) is used for the assessment of the expectedness of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials. Therefore, the RSI is a list of expected SARs, which are classified using preferred terms according to the MedDRA. An expectedness assessment is required to be conducted by the sponsor on each 'suspected' SAR to determine expedited reporting of 'suspected unexpected serious adverse reactions' (SUSARs), and for the identification of SUSARs in the cumulative summary tabulation of 'suspected' SARs in the Development Safety Update Report. Serious adverse events that may potentially occur due to the known MOA of odronextamab or due to potential class effects but have not been observed with the use of odronextamab as of the data cutoff, will not be included in the RSI section.

Table 37 shows expected SARs with odronextamab and should be used for assessing expectedness for regulatory reporting of individual SUSARs and for the identification of SUSARs in the cumulative summary tabulation of 'suspected' SARs in the Development Safety Update Report. This is based on the review of the available safety data with odronextamab monotherapy as of the data cutoff. All life-threatening or fatal SARs will be considered unexpected for regulatory reporting purposes.

Table 37: Serious Adverse Reactions for Odronextamab Considered Expected for Safety Reporting Purposes

MedDRA System Organ Class (SOC)	**SARs** **MedDRA Preferred Term**	**Patients treated (N=539)**
		SARs n* (%)
Immune system disorders	Cytokine release syndrome	118 (21.9)
Injury, poisoning, and procedural complications	Infusion related reaction	16 (3.0)
Metabolism and nutrition disorders	Tumour lysis syndrome	4 (0.7)
Infections and Infestations	Pneumonia	28 (5.2%)
	Pneumocystis jirovecii pneumonia	7 (1.3%)
	Cytomegalovirus infection reactivation	7 (1.3%)
	Cytomegalovirus infection	5 (0.9%)
	Respiratory tract infection	3 (0.6%)
	Pneumonia cytomegaloviral	3 (0.6%)
	Cytomegalovirus colitis	3 (0.6%)
	Herpes zoster	3 (0.6%)
	Sepsis	2 (0.4%)
	Septic shock	2 (0.4%)
	Bacteraemia	2 (0.4%)
	Cytomegalovirus viraemia	2 (0.4%)
	Pneumocystis jirovecii infection	2 (0.4%)

*n = number of patients who have experienced the serious adverse reactions (SARs)
1333-Adverse events were coded using MedDRA Dictionary 24.1, and graded using NCI-CTCAE version 4.03, except for CRS graded per adapted from Lee, 2014.
1625-Adverse events were coded using MedDRA Dictionary 24.1, and graded using NCI-CTCAE version 5.0., except for CRS graded per adapted from Lee et al, 2019.1504-Adverse events were coded using MedDRA Dictionary 20.0 and graded using NCI-CTCAE version 4.03.
Data cutoff date: 18 Sep 2022

7. OVERALL RISK AND BENEFIT ASSESSMENT

Odronextamab is a human bsAb based on an IgG4 isotype modified to further reduce Fc binding. Odronextamab is designed to bind to CD20-expressing target cells and to cross-link them to CD3-expressing T cells, resulting in local T cell activation and generation of an antigen nonspecific polyclonal cytotoxic T cell response. The cytotoxic T cell response seen with odronextamab is thus independent of the typical requirements for specific TCR recognition of a target cell. This MOA is distinct from that of currently available anti-CD20 antibody therapeutics and as such may also provide a therapeutic benefit in patients who have relapsed following anti-CD20 mAb therapy.

As of the data cutoff date 18 Sep 2022, 571 patients with B-lymphoid malignancies (B-NHL, CLL, and ALL cohorts) have been treated in the 3 studies with odronextamab monotherapy (539 patients), with an estimated patient exposure of 15039 weeks and in 1 study in combination with cemiplimab (32 patients) with an estimated patient exposure of 449.7 weeks.

Based on cumulative safety data with odronextamab and other T cell-engaging therapies, the important identified risks for odronextamab include CRS, IRR, infections and TLS and important potential risks include ICANS, systemic hypersensitivity, consequences of immunogenicity, and embryo-fetal toxicity. The Guidelines for the identification and management of important risks are described in the study documents (Protocols). The modified step-up regimen to further mitigate the risk of severe CRS events was successful in decreasing the incidence and severity of the CRS events.

7.1. Odronextamab Monotherapy

In view of the high response rates and durability of responses observed with odronextamab monotherapy (Table 30 and Table 31), the risk minimization measures in place for all important risks, as well as the safety data provided in this edition of the Investigator Brochure, justify continued clinical evaluation of odronextamab in patients with advanced B cell malignancies. As of 18 Sep 2022, there were no Grade ≥3 CRS events following implementation of the modified step-up regimen (0.7/4/20 mg) and other CRS risk minimization measures (Section 6.2.1).

Enrollment for patients with MCL and MZL is paused, until the partial clinical hold is lifted for cohorts with the MCL and MZL subtypes.

Pre-clinical and non-human primate studies indicate that SC administration of odronextamab may reduce the incidence of severe CRS while maintaining efficacy (R1979-TX-18196), supporting the planned clinical evaluation of SC administration of odronextamab in patients with advanced B cell malignancies.

7.2. Odronextamab in Combination with Cemiplimab

In view of the occurrence of the collective safety experience observed with odronextamab in combination with cemiplimab in patients with B-NHL, enrollment into this combination therapy study arm is on hold. Enrollment may resume after partial clinical hold has been lifted with appropriate risk minimization measures (See protocol for details).

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APPENDIX 1. SPONSOR LIST OF POTENTIAL ICANS TERMS MEDDRA 24.1

MedDRA PT terms for inclusion		
Acalculia	Encephalitis	Neurotoxicity
Action tremor	Encephalitis autoimmune	Noninfectious myelitis
Acute flaccid myelitis	Encephalitis brain stem	Noninfective encephalitis
Agitation	Encephalomyelitis	Noninfective encephalomyelitis
Agnosia	Encephalopathy	Oculofacial paralysis
Agraphia	Ependymitis	Optic neuritis
Altered state of consciousness	Essential tremor	Pachymeningitis
Amnesia	Facial paralysis	Palatal palsy
Amnestic disorder	Facial paresis	Panencephalitis
Anterograde amnesia	Generalized onset non-motor seizure	Papilloedema
Aphasia	Generalised tonic-clonic seizure	Paralysis
Aphonia	Glossopharyngeal nerve paralysis	Paraparesis
Apraxia	Hallucination	Paraplegia
Arachnoiditis	Hemiparesis	Paresis
Asterixis	Hemiplegia	Paresis cranial nerve
Ataxia	Hypoglossal nerve paralysis	Partial seizures
Aura	Hypoglossal nerve paresis	Postictal paralysis
Balance disorder	Hyporesponsive to stimuli	Postictal state
Borderline mental impairment	IIIrd nerve paralysis	Preictal state
Brain compression	IIIrd nerve paresis	Quadriparesis
Brain oedema	Immune effector cell-associated neurotoxicity syndrome	Quadriplegia
Brow ptosis	Immune-mediated encephalitis	Respiratory paralysis
Bulbar palsy	Immune-mediated encephalopathy	Retrograde amnesia
Central nervous system inflammation	Incoherent	Sedation
Cerebral arteritis	Intracranial pressure increased	Seizure
Cervical spinal cord paralysis	Irritability	Simple partial seizures
Change in sustained attention	IVth nerve paralysis	Slow speech
Clonic convulsion	IVth nerve paresis	Somnolence
CNS ventriculitis	Judgement impaired	Sopor
Cognitive disorder	Lack of spontaneous speech	Speech disorder
Cognitive linguistic deficit	Language disorder	Spinal cord paralysis

Coma	Lethargy	Stupor
Confusional state	Limbic encephalitis	Supranuclear palsy
Consciousness fluctuating	Loss of consciousness	Thoracic spinal cord paralysis
Cranial nerve paralysis	Lumbar spinal cord paralysis	Tongue paralysis
Delirium	Encephalitis	Tonic convulsion
Depressed level of consciousness	Encephalitis autoimmune	Transient aphasia
Diaphragmatic paralysis	Memory impairment	Transient global amnesia
Diplegia	Meningitis	Tremor
Disorganised speech	Meningitis aseptic	Trigeminal neuritis
Disorientation	Meningitis noninfective	Trigeminal palsy
Disturbance in attention	Mental impairment	Vagus nerve paralysis
Dyscalculia	Mental status changes	VIth nerve disorder
Dysgraphia	Monoparesis	VIth nerve paralysis
Dyskinesia	Monoplegia	VIth nerve paresis
Dysphonia	Myelitis	Vocal cord paralysis
Dyspraxia	Neuritis cranial	Vocal cord paresis

Listing as of 26 Oct 2021.

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