

Rapid Policy Statement

Interim Clinical Commissioning Policy: Casirivimab and imdevimab in the treatment of COVID-19 in hospitalised patients

4th November 2021

Commissioning position

The proposal is: Casirivimab and imdevimab is recommended to be available as a treatment option for COVID-19 through routine commissioning for hospitalised adults and children (aged 12 years and above) in accordance with the criteria set out in this document.

Background

Casirivimab and imdevimab is a neutralising monoclonal antibody (nMAB) combination that binds specifically to two different sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into the host cell and therefore inhibiting its replication.

The casirivimab and imdevimab combination is licensed in Great Britain for use in prophylaxis and treatment of acute COVID-19 infection. Ahead of a European Medicines Authority determination, use in Northern Ireland is covered by a regulation 174 approval. The conditional marketing authorisation was based on the following evidence:

- Study 2067 (Weinrich et al, 2021): a Phase 3 randomised, double-blinded, placebo-controlled trial evaluating casirivimab and imdevimab for the treatment of non-hospitalised patients with at least one risk factor for severe COVID-19. This showed that the casirivimab and imdevimab combination led to a relative risk reduction for composite primary outcome of COVID-19-related hospitalisation or all-cause death through day 29 by 70% ($p=0.0024$). The study showed similar treatment effects across patients treated with 2.4g and 1.2g doses of the combination.
- Study 2069 (O'Brien et al, 2021): this was a Phase 3 randomised, double-blind, placebo-controlled trial studying casirivimab and imdevimab for prevention of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case). The study population was stratified into two cohorts:
 - Cohort A comprised individuals with a negative SARS-CoV-2 PCR test result at baseline. Casirivimab and imdevimab led to a statistically significant 81% ($p<0.0001$) relative risk reduction in the development of symptomatic COVID-19 compared with placebo.

- Cohort B comprised asymptomatic individuals with a positive SARS-CoV-2 PCR test result at baseline. Casirivimab and imdevimab led to a statistically significant 31% ($p=0.038$) relative risk reduction in the development of symptomatic COVID-19 compared with placebo.

On 16 June 2021 the RECOVERY trial announced findings that casirivimab and imdevimab reduced the relative risk of mortality by 20% (24% in the treatment group vs 30% in those who received standard care alone) in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (were seronegative¹) at the time of treatment. A national expert group was convened and considered available evidence, including risk of hospital admission and mortality from COVID-19 in both community and hospitalised patients as per QCOVID3².

This rapid policy statement outlines the eligibility criteria for the use of casirivimab and imdevimab in hospitalised patients with COVID-19 in the following settings:

- 1) Patients hospitalised for acute COVID-19 illness: to be treated at the **off-label** dose of 2.4g
- 2) Patients with hospital-onset COVID-19: to be treated at a dose of 1.2g, in line with the conditional marketing authorisation

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria under one of the following pathways^{3 4}:

1) Patients hospitalised with acute COVID-19

Hospitalised patients are eligible to be considered for casirivimab and imdevimab if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis
- AND
- Hospitalised specifically for the management of acute symptoms of COVID-19⁵
- AND
- Negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2⁶ (see section on 'Serum antibody status' below)

2) Patients with hospital-onset COVID-19

Patients are eligible to be considered for casirivimab and imdevimab if:

¹ Refers to patients who were negative for serum antibodies against SARS-CoV-2

² QCOVID3 is a population-based cohort study performed to derive and validate a risk prediction algorithm to estimate hospital admission and mortality outcomes from COVID-19 in adults in England. Additional work was undertaken by the QCOVID team on risk of death in hospitalised patients.

³ For paediatric patients (aged 12-17 years inclusive), paediatric MDT assessment may be deemed necessary to determine clinical capacity to benefit from the treatment.

⁴ Clinical judgement should be applied in making treatment decisions, and may be guided by validated decision support tools such as the ISARIC-4C Mortality and Deterioration Scores

⁵ Eligible patients will be acutely ill and admitted specifically to manage symptoms of COVID-19 infection or if COVID-19 infection has been contracted during the hospital stay, symptoms are such that they would have otherwise prompted a hospital admission, independent of the other reasons for the patient's current admission.

⁶ The RECOVERY trial population tested patients specifically for anti-S antibodies

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test **within the preceding 72 hours** or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis
AND
- Hospitalised for indications other than for the management of acute symptoms of COVID-19;
AND
- At high risk of progression to severe COVID-19 (see Appendix 1 for list of qualifying conditions)
OR
COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team [MDT] assessment)
AND
- A baseline serum antibody test (anti-S) against SARS-CoV-2 prior to treatment administration has been taken (see ‘Data collection requirement’ section).

Patients in Group 2) that have been treated with casirivimab and imdevimab that continue to deteriorate such that their acute COVID-19 illness requires hospital-based care are eligible for a second dose of casirivimab and imdevimab if they fulfil the criteria for Group 1) above (see also the “Dose” section below).

Exclusion criteria

The following patients are not eligible for treatment:

- Children weighing less than 40kg
- Children aged under 12 years
- Known hypersensitivity reaction to the active substances or to any of the excipients of casirivimab and imdevimab listed in the [Summary of Product Characteristics \(SmPC\)](#)
- Previously received treatment in hospital with casirivimab and imdevimab at the 2.4g (combined) dose or higher during this course of infection

Serum antibody status

Patients may be tested for anti-S1 or anti-S2 antibodies using any validated quantitative or qualitative anti-S assay that measures either IgG or total antibody levels. Serostatus should be established in line with the pre-determined thresholds relevant to the assay being used by the testing laboratory. Quantitative assays with pre-specified thresholds for seropositivity should return clear binary (i.e. either ‘negative’ or ‘positive’) results based on these thresholds. For quantitative assays without a formal threshold for serostatus, clinical decision-making should guide treatment decisions.

In immunocompromised groups, very low ‘positive’ levels of anti-S antibody on a quantitative assay (within the bottom 10% of the assay’s positive range) should be interpreted in the context of clinical decision-making and laboratory advice and a decision to treat may still be made by the MDT on a case-by-case basis. Providers will be required to report anti-S

antibody levels in treated patients, and the corresponding reference range of the local assay, for central monitoring.

In immunodeficient patients on replacement immunoglobulin (intravenous or subcutaneous), the positive detection of anti-S antibodies should be regarded as a 'positive of unknown significance'. Patients on replacement immunoglobulin testing positive only for anti-S (and negative for anti-N antibodies) should therefore be considered to be seronegative for SARS-CoV-2, and MDT assessment should judge their eligibility for nMAB treatment. Should evidence for passive transmission of anti-N antibodies through replacement immunoglobulin emerge in the future, the detection of anti-N antibodies should also be regarded as a 'positive of unknown significance'.

If there are concerns or questions around laboratory sensitivity or cut-offs these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from the EQA scheme participation.

Cautions

Please refer to the [Summary of Product Characteristics \(SmPC\)](#) for casirivimab and imdevimab for special warnings and precautions for use.

The casirivimab and imdevimab combination is not intended to be used as a substitute for vaccination against COVID-19.

COVID-19 vaccines

Casirivimab and imdevimab binds to epitopes on spike protein used as immunogen in all COVID-19 vaccines, therefore it is possible that casirivimab and imdevimab may interfere with the development of effective immune responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post treatment with anti-SARS-CoV-2 monoclonal antibodies. Limited safety data are available from the study HV-2093 where COVID-19 vaccine was permitted, and no safety concerns were identified.

Further information on the timing of COVID-19 vaccination following administration of casirivimab and imdevimab is available at the following sites:

- [Liverpool COVID-19 Interactions \(covid19-druginteractions.org\)](https://covid19-druginteractions.org/)
- [Interactions information for COVID-19 vaccines – SPS - Specialist Pharmacy Service](#)

Pregnancy and women of childbearing potential

The RECOVERY trial included women who were pregnant or breastfeeding, and no serious adverse events were reported. The SmPC for casirivimab and imdevimab states the following:

"Pregnancy

There are no or limited amount of data from the use of casirivimab and imdevimab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. In a tissue cross-reactivity study with casirivimab and imdevimab using human foetal tissues, no binding was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing foetus. Casirivimab and imdevimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother

and the foetus considering all associated health factors. If a woman becomes pregnant while taking this medicine, the individual should be informed that any potential risk to the foetus is unknown.

Breast-feeding

It is unknown whether casirivimab and imdevimab are excreted in human milk. A risk to the newborns/infants cannot be excluded. Maternal IgG is known to be present in human milk and any potential risk of adverse reactions from the drug in breast-feeding infants is unknown, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from casirivimab and imdevimab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. Breast-feeding mothers with COVID19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.”

Dose

1) Patients hospitalised with COVID-19

The recommended dose of casirivimab and imdevimab is 2.4g⁷ (1.2g each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion⁸.

Please note that the use of casirivimab and imdevimab in patients hospitalised with COVID-19 at the 2.4g dose is off-label.

2) Patients with hospital-onset COVID-19

The recommended dose of casirivimab and imdevimab is 1.2g (600mg each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion^{8,9}.

Patients may be eligible for a 2.4g repeat dose if they continue to deteriorate such that their acute COVID-19 illness requires hospital-based, providing they fulfil the eligibility criteria for Group 1) above.

Administration

Preparation and administration of casirivimab and imdevimab should be initiated and monitored by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice.

Infusion solutions should be made up according to the following table:

Dose	Active substance	Diluent	Infusion time
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⁷ This dose for hospitalised patients was recommended by consensus of an expert group, based on available research and other pharmacokinetic data.

⁸ No dose adjustment is recommended in patients with renal impairment. The pharmacokinetics of casirivimab and imdevimab have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment.

⁹ The 1.2g dose may also be delivered via the subcutaneous route; please refer to the SmPC for further information.

2.4g	1.2g (10ml of 120mg/ml) of casirivimab and 1.2g (10ml of 120mg/ml) of imdevimab Total dose volume: 20ml	250mls of 0.9% sodium chloride	30 minutes (minimum)
1.2g	600mg (5ml of 120mg/ml) of casirivimab and 600mg (5ml of 120mg/ml) of imdevimab Total dose volume: 10ml	250mls of 0.9% sodium chloride	30 minutes

Refer to the Specialist Pharmacy Services [institutional readiness document](#) for further information on the handling, reconstitution and administration of the product.

Casirivimab and imdevimab should not be infused concomitantly in the same intravenous line with other medication. Repeat doses should not be administered.

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions (IRRs) have been observed with IV administration of casirivimab and imdevimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Co-administration

Corticosteroids

Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found [here](#). Casirivimab and imdevimab should not be regarded as an alternative to corticosteroids.

There is no interaction of casirivimab and imdevimab with either dexamethasone or hydrocortisone expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (<https://www.covid19-druginteractions.org/checker>).

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 can be found [here](#). There is no interaction of casirivimab and imdevimab with remdesivir expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (<https://www.covid19-druginteractions.org/checker>).

IL-6 inhibitors

The Clinical Commissioning Policy for the use of IL-6 inhibitors (tocilizumab or sarilumab) in hospitalised patients with COVID-19 who require supplemental oxygen can be found [here](#).

There is no interaction of IL-6 inhibitors with casirivimab and imdevimab expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (<https://www.covid19-druginteractions.org/checker>).

Safety reporting

Any suspected adverse reactions from treatment with casirivimab and imdevimab should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: <https://coronavirus-yellowcard.mhra.gov.uk/>.

Marketing authorisation

Casirivimab and imdevimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in prophylaxis and treatment of acute COVID-19 infection. Access to casirivimab and imdevimab in Northern Ireland for the above indications is through a Regulation 174 approval ahead of a licensing determination by the European Medicines Agency.

The use of casirivimab and imdevimab in patients at a dose of 2.4g is off-label, while its use at the 1.2g dose is within the conditional marketing authorisation.

Governance

Off-label use of medication

Any provider organisation treating patients with these interventions will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

All patients being considered for treatment with casirivimab and imdevimab for COVID-19 during their hospital stay should have their baseline serum antibody (anti-S) status measured prior to treatment to enable further evidence generation around the differential impact of treatment based on serology status.

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Clinicians are also required to ensure that any data collection requirements are met for the purpose of ongoing surveillance, audit and relevant evaluation, including of clinical effectiveness, around the use of nMABs (see 'Surveillance and service evaluation' section below).

Clinical outcome reporting

It is vital to be able to monitor the clinical progression of patients treated with nMABs. Hospitals managing COVID-19 patients are strongly encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (<https://isaric4c.net/protocols/>). In addition, completion of the Blueteq forms (in England) will

provide further essential data. Intermittent blood sampling (sparse sampling) may be required to collect serum concentration data. There will be a standard operating procedure circulated on sparse sampling to monitor serum concentration levels with nMAB treatment.

Effective from

This policy will be in effect from the date of publication.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of casirivimab and imdevimab for COVID-19 would supersede this policy when completed.

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of nMABs in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB treatment; the impact of nMAB treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB use, such as generation of new mutations.

Treating clinicians are asked to ensure that all PCR tests undertaken as an inpatient and/or in the community where any patient who is receiving ongoing PCR testing as part of secondary care (for example, through an outpatient clinic) should do this through the hospital laboratory where these samples should be retained for sequencing. At present, no further serial sampling is requested for UKHSA purposes, however this may change once clinical and infection control guidance in this area has been renewed in line with the latest evidence.

Clinicians must ensure that any additional data collection requirements are met for the purpose of relevant surveillance, audit and evaluation around the use of nMABs. It is expected that there will be ongoing monitoring (involving sample collection) of selected patients treated with nMABs (led by Public Health England/UK Health Security Agency, for instance around the potential generation of new variants), as well as academic research to generate new knowledge around clinical effectiveness and other relevant aspects of public health.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
Neutralising monoclonal antibody	Synthetic antibodies that bind to a virus and inhibit its ability to infect host cells and replicate
Spike protein	The part of the SARS-CoV-2 virus that binds to the host cell, which then facilitates its entry into the cell
Anti-S antibody	Antibodies directed against the spike protein of the SARS-CoV-2 virus

References

1. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med.* 2021;385(13):1184-1195. doi:10.1056/NEJMoa2109682
2. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial
3. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19 [published online ahead of print, 2021 Sep 29]. *N Engl J Med.* 2021;NEJMoa2108163. doi:10.1056/NEJMoa2108163

Appendix 1

The following patient cohorts are considered to have impaired immune function, be at significant risk of an adverse COVID-19 outcome, and have a high clinical capacity to benefit from treatment with nMABs. This list of conditions below, generated through consensus of clinical experts, is not exhaustive and other causes of impaired immune function may be deemed apt for treatment with nMABs by MDT assessment.

1. Primary immunodeficiency

- Common variable immunodeficiency (CVID)
- Undefined primary antibody deficiency on intravenous immunoglobulin (IVIg) (or eligible for IVIg treatment)
- Hyper-IgM syndromes
- Good's syndrome (thymoma plus B-cell deficiency)
- Severe Combined Immunodeficiency (SCID)
- Autoimmune polyglandular syndromes/Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- Primary immunodeficiency associated with impaired type I interferon signalling
- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)

2. Secondary Immunodeficiency

- Any secondary immunodeficiency patient requiring immunoglobulin replacement therapy
- Haematological malignancies
 - Chronic lymphocytic leukaemia (CLL)
 - B-cell lymphoma
 - Follicular lymphoma
 - Waldenstrom's macroglobulinaemia
- Multiple myeloma
- Post-CAR-T cell therapy for B-acute lymphoblastic leukaemia and B-cell lymphoma
- Recipients of rituximab or other CD20 depleting monoclonal antibodies (such as ofatumumab and ocrelizumab)
- Patients on conventional immunosuppressive therapy across rheumatology, neurology, dermatology, nephrology and gastroenterology
- Patients on other biologics such as abatacept and small molecule JAK-inhibitors (such as and tofacitinib, baricitinib)
- Patients receiving chronic high-dose corticosteroid therapy: >20mg (0.5mg/kg) prednisolone (or equivalent) per day for more than four weeks
- Recipients of solid organ, bone marrow or stem cell transplants (irrespective of time since transplant or use of immunosuppressive medications)

3. Patients with any of the following diagnoses:
 - Down's syndrome
 - Sickle cell disease
 - Chronic kidney disease (stage 5)
 - HIV/AIDS (irrespective of viral load or CD4 count)
 - Liver cirrhosis
 - Rare neurological conditions such as motor neurone disease, multiple sclerosis, myasthenia gravis or Huntington's chorea
4. Patients who have received radiotherapy in the last 6 months
5. Patients currently on or have received the following chemotherapy regimens (Groups B and C in the table below) in the last 12 months and are considered to be at higher risk of Grade 3/4 febrile neutropenia or lymphopenia

Group B	Group C
10-50% risk of grade 3/4 febrile neutropenia or lymphopenia	>50% risk of grade 3/4 febrile neutropenia or lymphopenia
<ul style="list-style-type: none"> ● Etoposide based regimens ● CMF ● Irinotecan and Oxaliplatin based regimens ● Cabazitaxel ● Gemcitabine ● Chlorambucil ● Temozolomide ● Daratumumab ● Rituximab ● Obinutuzumab ● Pentostatin ● Proteasome inhibitors ● IMiDs ● PI3Kinase inhibitors ● BTK inhibitors ● JAK inhibitors ● Venetoclax ● Trastuzumab-emtansine ● Anthracycline-based regimens ● Fluorouracil, epirubicin and cyclophosphamide (FEC) ● Methotrexate, vinblastine, adriamycin/doxorubicin, cisplatin (MVAC) ● Adriamycin/doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) ● Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) ● Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) ● Liposomal doxorubicin ● Taxane – 3-weekly ● Nab-paclitaxel ● Carboplatin-based regimens ● Ifosfamide-based regimens ● Bendamustine 	<ul style="list-style-type: none"> ● All acute myeloid leukaemia/acute lymphocytic regimens ● Bleomycin, etoposide and platinum ● Highly immunosuppressive chemotherapy (e.g. FluDAP, high dose Methotrexate & Cytarabine) ● Trifluradine/ Tipiracil ● KTE-X19 ● Gilteritinib

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| <ul style="list-style-type: none">• Cladribine• Topotecan• Cyclophosphamide/Fludarabine combinations• Ifosfamide, carboplatin, etoposide (ICE)• Gemcitabine, dexamethasone, cisplatin (GDP)• Isatuximab• Polatuzumab• Acalabrutinib• Dexamethasone, cytarabine, cisplatin (DHAP)• Etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP)• Cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD)• Dacarbazine-based regimens• Lomustine• Magalizumab• Brentuximab vedotin• Asparaginase-based regimens | |
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