Transfusion management of patients treated with monoclonal antibody (MAb) therapies that interfere with immunohaematology testing

Addendum to ANZSBT *Guidelines for Transfusion and Immunohaematology Laboratory Practice (revised 1st edition; January 2020)* (https://anzsbt.org.au/guidelines-standards/anzsbt-guidelines/).

This addendum is intended to guide laboratories in provision of compatible blood for transfusion. It applies to *Section 2 Pretransfusion testing*, and *Section 3 Selecting Blood Products for Transfusion*, *Section 4 Use of blood products in specific clinical situations* of the guidelines.

PRIOR TO TREATMENT with therapeutic monoclonal antibody therapy (MAb)	**CLINICIAN** 1. Communicate with testing laboratory that a patient is to commence on specified MAb – expect a longer turnaround time as additional pretransfusion testing is required, and in some cases referral to a reference laboratory. 2. Order 'group and screen', extended red cell phenotype; note on request that patient is to commence on MAb and specify therapy being used. 3. Provide patient with an alert card as per institutional policy.[1] **LABORATORY TESTING** 1. Blood group (ABO and RhD) – resolve any discrepant results. 2. Antibody Screen (IAT) – identify any pre-existing antibodies 3. Antigen typing: Rh (C, c, E, e), K (k if K+), Jk^a, Jk^b, Fy^a, Fy^b, S, s, is recommended as minimum. Perform: a. Phenotype if patient not transfused in last 3 months b. Genotype if patient transfused in last 3 months or has positive DAT. 4. Note on patient laboratory record (LIMS) the therapy, date and treating clinician.
URGENT TRANSFUSIONS (Blood required <2 hours)	Issue blood using institutional protocols for emergency transfusion: 1. Group O emergency red cells. 2. If time allows, select antigen negative red cells matched to patient phenotype. 3. Request Group and Screen sample to be taken prior to transfusing for retrospective testing and crossmatching. **Notes:** • Transfusing O emergency red cells is not without risk, and may not be suitable in all circumstances, i.e., patient has historic antibodies. • Red cells must not be issued based on a historic blood group. • If patient is on anti-CD38 select Kell neg units.

NON-URGENT TRANSFUSIONS	**CLINICIAN** Plan transfusions in advance and liaise with testing laboratory for provision of Red Cells. **LABORATORY TESTING** 1. Perform blood group: a. Results are concordant with patient's pre-treatment group - no further testing of group is required. b. Results are not concordant / discrepant with patient's pre-treatment group - refer to box below for specific MAb. 2. Perform IAT antibody screen: a. Negative result – no further test investigation required, proceed as per usual institutional policy. b. Positive result – refer to box below for specific MAb.
ANTI-CD38 i.e. daratumumab, isatuximab	CD38 is expressed on red cells. Anti-CD38 binds to red cells and causes interference with pretransfusion IAT testing.[1,2] The result is a positive antibody screen and sometimes a positive DAT. To determine if there are underlying antibodies, reagent red cells can be treated with dithiothreitol (DTT) or with trypsin to denature cell surface CD38. Cells can then be used for antibody screen/identification. Some antigens, notably Kell system antigens, are denatured by DTT. 1. Positive antibody screen (generally 1+ to 2+; using 0-4 scoring) with all cells - treat reagent cells with DTT/trypsin or refer sample to a reference laboratory. 2. Retest with DTT or trypsin treated screen/antibody panel cells* a. If screen is negative, proceed as per institutional policy. b. If screen has positive reactions, identify antibody using DTT/trypsin treated panel cells. 3. If patient has antibody/s (or history of), donor red cells negative for the corresponding antigen should be selected. 4. If antibody/s unable to be identified, select red cells that are compatible with extended phenotype matching. Alert haematologist. 5. Full IAT crossmatch will be positive unless donor cells are DTT / trypsin treated. **Notes:** * Use of other validated laboratory methods to reduce interference may assist with antibody identification. • Due to the potential complexity of, or difficulties associated with, pretransfusion testing in cases of monoclonal antibody therapy, it may be necessary to refer the specimen to a reference laboratory.

ANTI-CD47 e.g. magrolimab	CD47 is expressed on red cells as part of the Rh complex.[3] Anti-CD47 binds to red cells and causes interference with pretransfusion immediate spin and IAT testing. This may cause false positive results in the reverse group, the antibody screen and sometimes a positive DAT. Magrolimab is a monoclonal IgG4 antibody. To determine if there are underlying antibodies IAT testing may be performed using an AHG reagent that does not detect human IgG subclass 4 (IgG4)*. 1. Perform blood group. If the result is not concordant for group, select group O RhD matched red cells. 2. Antibody Screen positive: repeat test using AHG that does not detect IgG4. a. If negative using AHG (minus anti-IgG4), proceed as per usual protocol. b. If positive reactions, identify antibody/s. 3. If patient has antibody/s (or history of), donor red cells negative for the corresponding antigen should be selected. 4. Perform crossmatch by IAT using AHG (minus anti-IgG4). 5. If antibody unable to be identified, select red cells with extended phenotype matching. Alert haematologist. **Notes:** * Not all anti-CD47 MAbs are IgG4. • Repeated alloadsorptions of the patient's plasma may assist in removing interference in the antibody screen, however this technique is not widely available in transfusion laboratories.[3] • Due to the potential complexity of, or difficulties associated with, pretransfusion testing in cases of monoclonal antibody therapy, it may be necessary to refer the specimen to a reference laboratory.
RED CELL SELECTION AND ISSUE	1. ABO blood group: a. Resolved – select the same group as patient, if unavailable a compatible ABO blood group is permissible. b. Not resolved – select group O red cells and follow institutional policy. 2. Antibody screen: a. Negative and no history of clinically significant antibodies – provide phenotype matched red cells. b. Positive or patient has history of antibody/s - donor red cells negative for the corresponding antigen/s should be selected, and if able, crossmatched by IAT using method described for specified MAb. 3. Laboratories unable to perform specialised testing may elect to follow institutional protocol for provision of extended phenotype matched red cells. **Notes:** • Carryover to subsequent samples has been observed on analysers. • Where phenotype matched units are not readily available, discuss with the clinical team. • In absence of alloantibodies priority order: Rh > K > Jk > Fy > Ss matching.

GENERAL NOTES	**Red cell genotyping** services are currently provided by the Australian Red Cross Lifeblood and New Zealand Blood Service. Follow protocol on websites: ARCLB: https://transfusion.com.au/resource_centre/forms NZBS:https://nzbs.centralstation.co.nz/Clinical-information/Technical-services/Reference-Laboratory/Investigations-undertaken

Abbreviations:
AHG: anti-human globulin; DAT: direct antiglobulin test; DTT: Dithiothreitol; IAT: indirect antiglobulin test; IgG: immunoglobulin G; LIMS: laboratory information management system; MAb: monoclonal antibody.

References:

1. Quach H et al. Considerations for pre-transfusion immunohaematology testing in patients receiving the anti-CD38 monoclonal antibody daratumumab for the treatment of multiple myeloma. IMJ 2018; 48: 210-220
2. Chapuy C et al. Resolving the daratumumab interference with blood compatibility testing. Trans 2015; 55:1545-1554
3. Velliquette R et al. Monoclonal anti-CD47 interference in red cell and platelet testing. Trans 2019; 59:730-737
4. British Standards in Haematology Managing patients who are being treated with targeted therapeutic monoclonal antibodies. Addendum cited 18th April 2021 v2 27/3/17: https://b-s-h.org.uk/media/15725/monoclonal-antibodies-addendum.pdf