Validation of In-house Antibody screening and Crossmatching of Daratumumab patients

EAMON CLAVIN, FABIAN MCGRATH, ALISON HARPER,

PROF HELEN ENRIGHT

TALLAGHT UNIVERSITY HOSPITAL, TECHNOLOGICAL UNIVERSITY DUBLIN

Multiple Myeloma

- Malignancy of a single clone of mature plasma cell.
- Incidence of 3.6-6.3 cases per 100,000 in the Republic of Ireland in 2016.
- Non-linear disease progression.
- Overproduction of monoclonal antibodies, infiltration of bone marrow and tissues, metabolic disturbances.
- Characteristic CRAB symptom profile: hypercalcaemia, renal impairment, anaemia and bone degradation.
- Monoclonal gammopathy leads to immunosuppression and infection- leading cause of death.

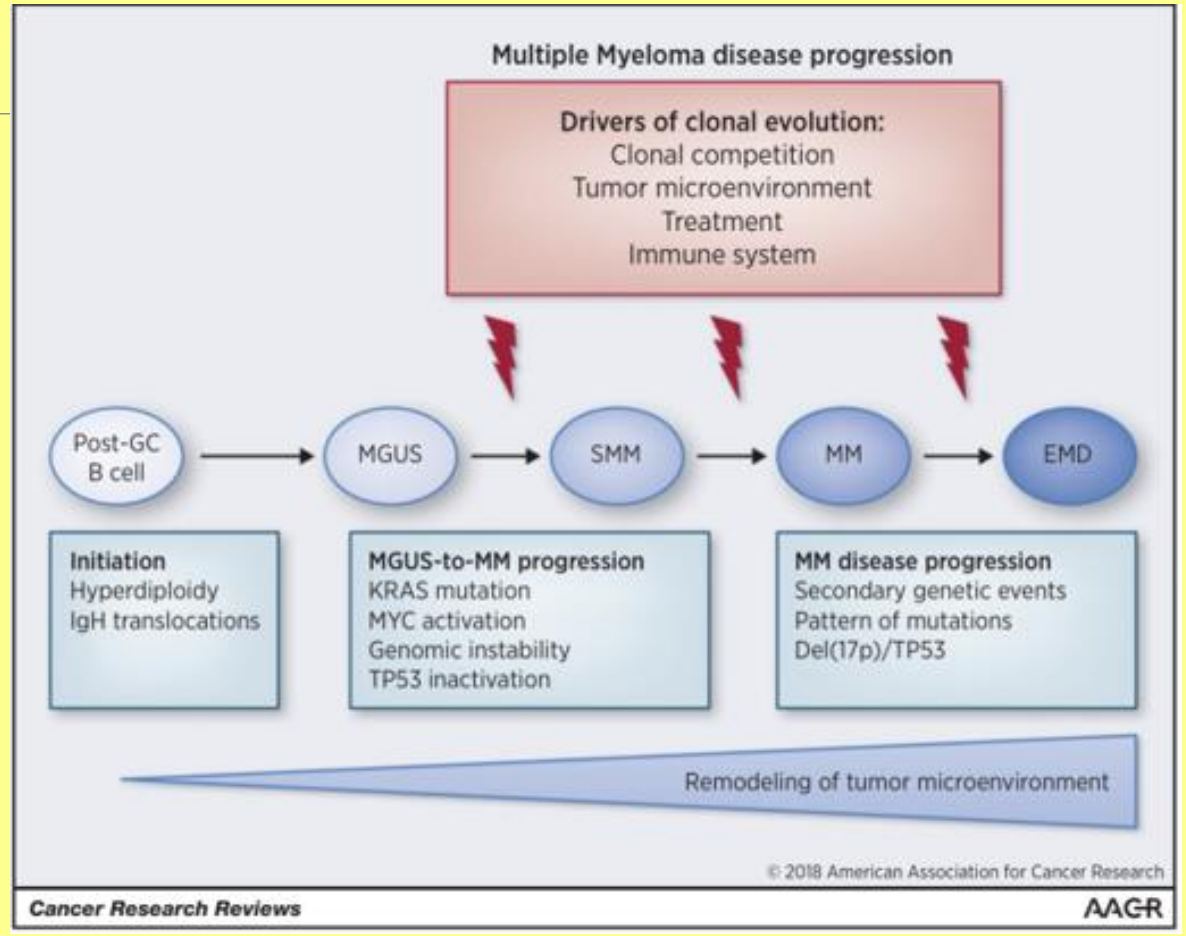


Figure 1: Progression of multiple myeloma

Treatment

AUTOLOGOUS HAEMOPOIETIC STEM CELL TRANSPLANTATION (ASCT)

- Harvesting of patient's own haemopoietic stem cells.
- Conditioning of patient- High intensity Chemotherapy.
- Re-infusion of patient's haemopoietic stem cells and re-engraftment.
- Patient is transfusion dependent and immunocompromised.

PHARMACOLOGICAL TREATMENT

- Proteasome inhibitors- Bortezomib
- Corticosteroids- Dexamethosone
- Immunomodulatory drugs- Lenalidomide
- Novel Immunotherapies- Anti-CD38, Daratumumab (DARA), Isatuximab

The CD38 Antigen

- Transmembrane ADP-cyclase, 300 AA in length.
- Contains 12 Disulphide bridges.
- Highly expressed on MM cells.
- May disrupt T-cell activation by interacting with CD31 in Immunological synapse.
- ADP Ribose and Cyclic ADP Ribose produced promote B-cell/plasma cell proliferation.
- Expression also present on NK cells, T-Reg cells and RBCs

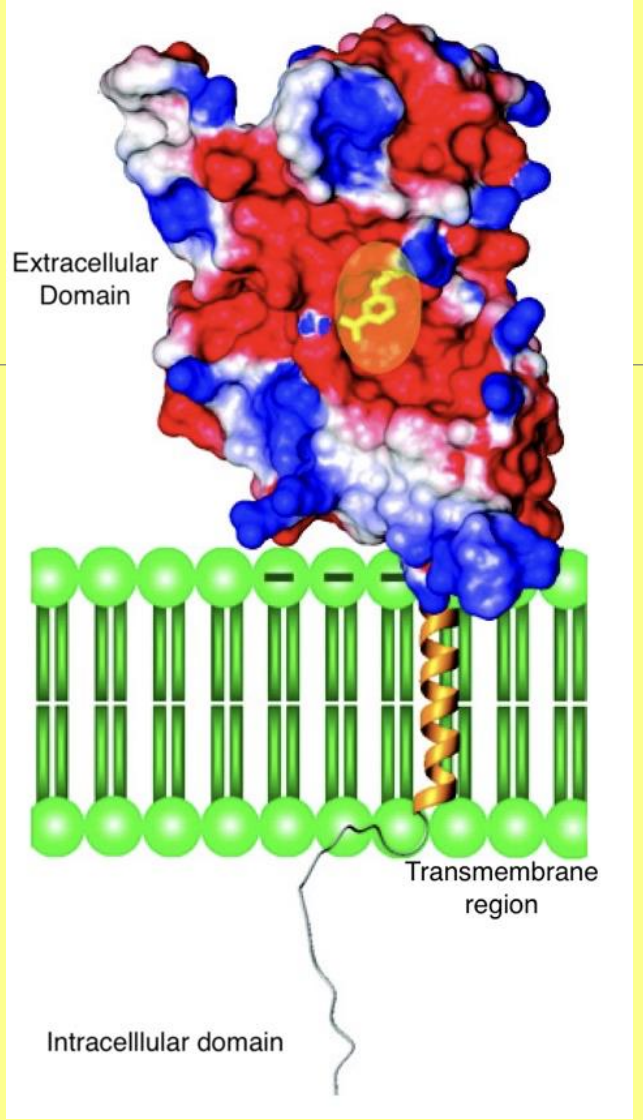


Figure 2: structure of the CD38 antigen

Daratumumab: Anti-CD38

- Monoclonal antibody therapy first licensed for use in 2015.
- Manufactured by Johnson and Johnson (Janssen) under trade name Darzalex.
- Human IgGk derived from Chinese hamster Ovary cell lines for therapeutic use
- IgG antibody against CD38- Transmembrane ADP-cyclase highly expressed on Plasma cells.
- Multiple modes of anti-MM cell activity: complement fixation, Fc receptor engagement, suppression of Treg response.

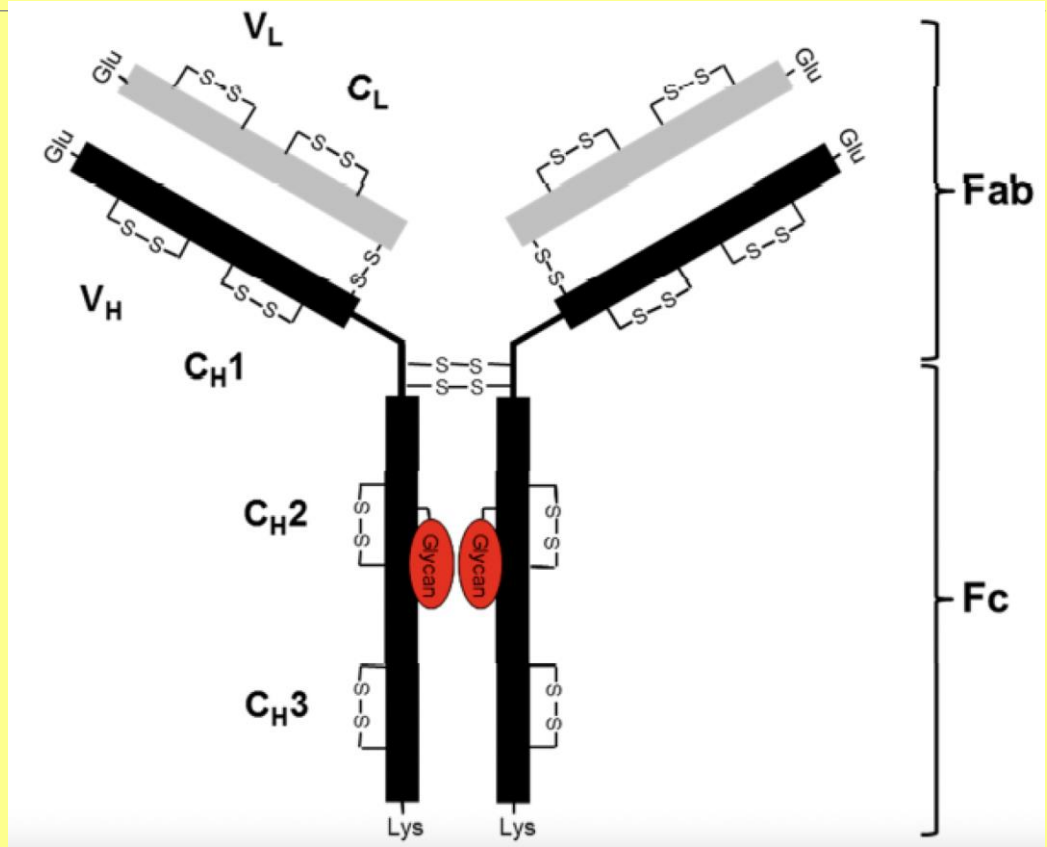


Figure 3: structure of the Daratumumab monoclonal antibody (Janssen 2017)

Daratumumab Mechanisms of Action

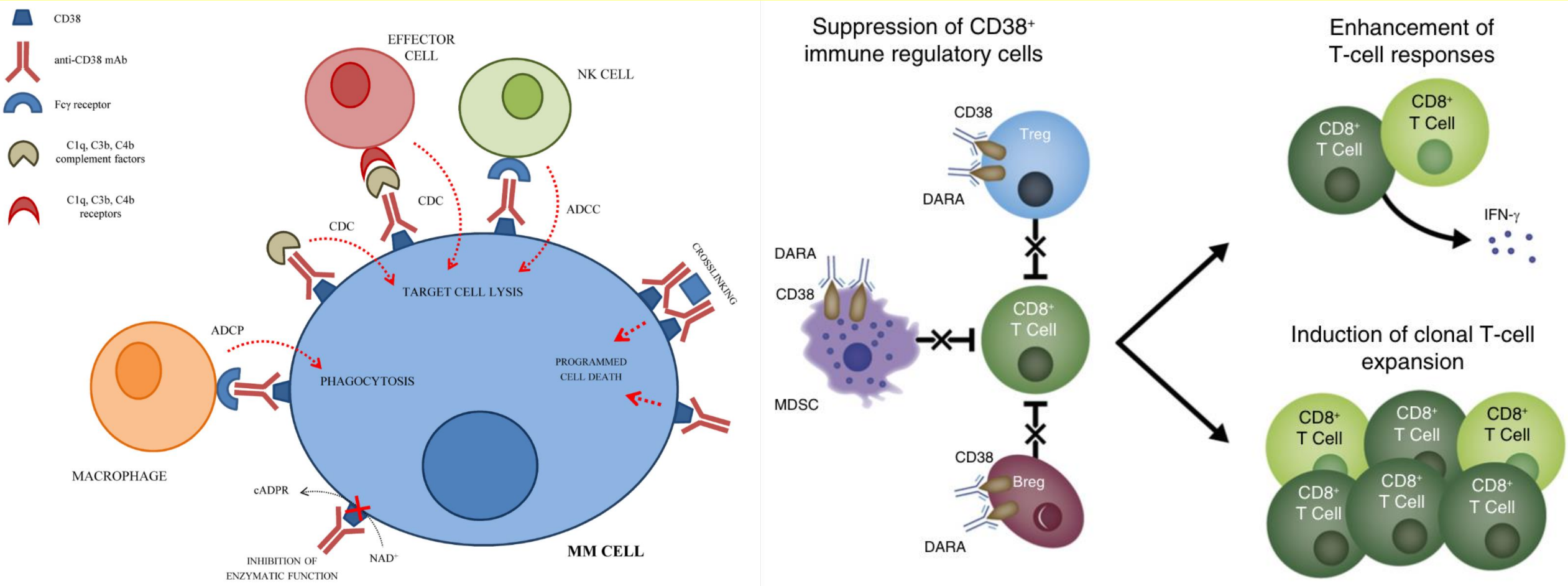


Figure 4 : Mechanisms of MM cell destruction by Daratumumab (Morandi et al. 2018)

Indications and Efficacy of Daratumumab

- Initially indicated for use as a ”last resort” monotherapy for relapsed/Refractory MM
- SIRIUS clinical Trial: OR in 29% of patients, clinical benefit in 34% of patients.
- Indications for use updated in 2019: DARA suitable for use in combination with other drugs.
- Superior complete response of newly diagnosed MM patients receiving regimens containing DARA (48%) vs conventional therapy (26%).
- Drop in Hb (up to 16g/L) and neutrophils common on commencement

Previous Treatment	ASCT Eligibility	Drugs used in combination with Daratumumab
≥ One Prior Therapy	Ineligible	Lenalidomide + Dexamethasone
None (Newly Diagnosed)	Ineligible	Bortezomib + Melphalan + Prednisone
None (Newly Diagnosed)	Eligible	Bortezomib + Thalidomide + Dexamethasone
≥ One Prior Therapy	Unspecified	Bortezomib + Dexamethasone
≥ Three Prior Therapies	Unspecified	Carfilzomib + Dexamethasone
≥ Two Prior Therapies including lenalidomide and a proteasome inhibitor	Unspecified	Pomalidomide + Dexamethasone

Interference in Pre-Transfusion Testing

- Indirect Antiglobulin Test- basis for antibody screening and ID, and crossmatching.
- Daratumumab binds to CD38 antigen on reagent or donor unit red cells.
- Causes false positive IAT with Panreactive pattern, variable effects on DAT.
- Risk of masking clinically significant red cell antibodies.
- Automated platforms: Reports of carryover of reactivity from daratumumab plasma samples into non-daratumumab samples.
- Interference up to 6 months after stopping therapy.

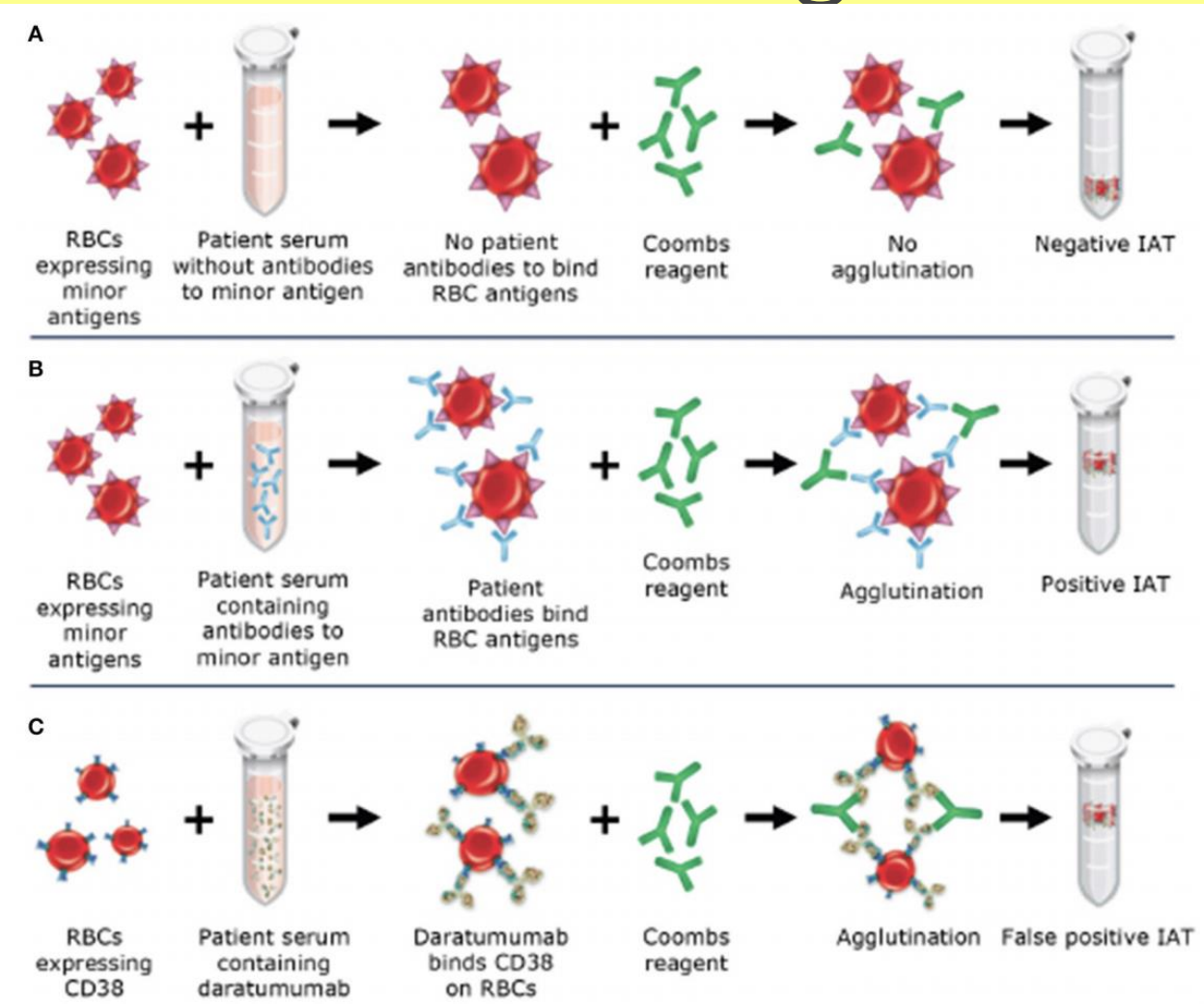


Figure 5:Interference of DARA in IAT-Based tests (Lancman et al 2018

Addressing Daratumumab Interference

- Soluble CD38 and Dara-Fab Fragments- Neutralise Daratumumab or mask CD38 on red cells – expensive.
- Dithiothreitol (DTT) treatment of red cells- Inexpensive, widely used, employed by IBTS.
- DTT- Reducing agent that cleaves Disulphide bridges within proteins.
- Red cells treated with DTT at pH 8.0 are functionally CD38 negative.
- Also removes blood group antigens containing disulphide bonds: Kell, Lutheran, India, Dombrock, Cromer.

Daratumumab In Tallaght University Hospital

PRIOR TO DARATUMUMAB THERAPY

- Samples obtained for Group and save, DAT and Rh/K analysis.
- Patients flagged to receive CMV- Irradiated ABO Rh/K matched red cells
- Samples referred to IBTS for genotyping for Rh, Kell, Duffy, Kidd, MNS

FOLLOWING COMMENCEMENT OF THERAPY:

- Group and crossmatch samples referred to IBTS: suitable units received ≈24 hours later
- For Platelet issue: Group and save samples processed every 2 weeks using **Manual Methods Only**

New Indications: Implications for TUH

- Estimated increase in DARA patients from Five patients per year to 15 patients per year.
- Estimated annual cost of referral of Daratumumab samples to IBTS for crossmatching: €306,196.80.
- IBTS referral service mainly operational during routine hours.
- Due to unknown risk of analyser carryover, accidental automated processing of DARA renders subsequent patient samples unsuitable for crossmatching- new samples required.

Objectives of this Study

- Determine risk of carryover associated with automated processing of Daratumumab samples.
- Mitigate anti-CD38 interference in IAT-based Antibody screening and crossmatching using DTT-treatment of reagent/donor red cells
- Detect underlying antibodies in Daratumumab plasma Via IAT-based antibody screening and crossmatching using DTT-treatment of reagent/donor red cells

Sample Procurement

- EDTA whole blood samples from known DARA patients.
- Samples obtained were those that were not processed or processed in-house as part of routine patient care.
- Procurement of archived samples took place between October 2019 and December 2020.
- Total of 59 samples procured from four patients- five contained no DARA, One had an insufficient volume for analysis.

Study Design

- Analyser Carryover Study
- Quantitation of DARA.
- DTT treatment of Red cells
- Mitigation of DARA interference in IAT crossmatching and antibody screening using DTT-treated red cells.
- Detection of underlying antibodies in samples containing DARA via IAT crossmatching and antibody screening using DTT-treated red cells.

Analyser Carryover Study

- Performed using Ortho Vision Max analyser- Column Agglutination Technology.
- Sequential antibody screening of Dara samples using Surgiscreen screening cells.
- Ortho AB Whole blood control run after each sample- negative control.
- DAT performed on WB control after every 10 DARA samples
- Analyser carryover defined as:
  - Positive screen observed with WB control

    or

  - Positive DAT observed on WB control RBCs

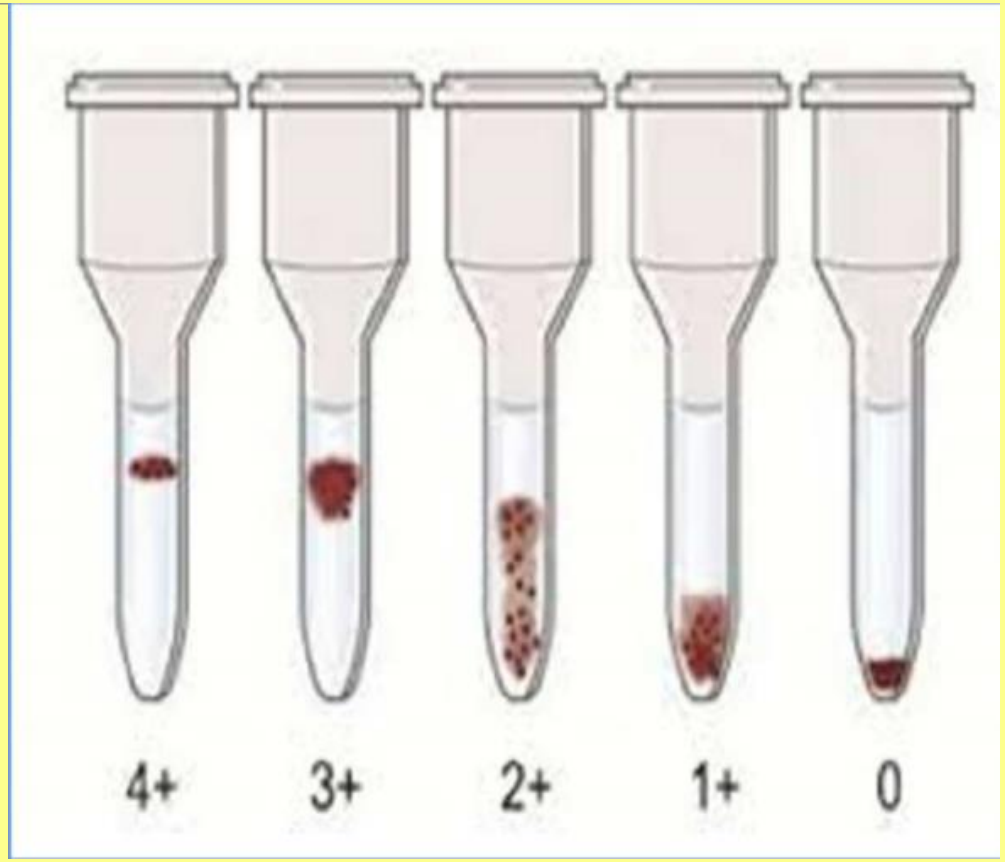


Figure 6: Grading criteria for CAT-based testing

Daratumumab Quantitation

- Performed to estimate abundance of DARA in each sample.
- Performed using Ortho Vision Max analyser.
- Serial dilutions of DARA plasma in PBS at dilutions of 1:1- 1:1024 and tested against a Surgiscreen Screening cell Via IAT.
- Inverse of lowest dilution at which 1+ reaction occurred taken as Dara Titre.

DTT-Treatment of red cells

- Batches of Grifols Screencyte Screening cells and Donor Unit red cells treated using 0.2M DTT at pH 8.0
- 400µl of RBCs washed four times in PBS pH 7.3
- Incubated with 2000µl DTT @37 degrees for 40 minutes with agitation.
- Washed four times in PBS pH7.3- made up to 3-5% suspension.
- Screening cells with known expression of K and E antigens phenotyped using anti-E and Anti-K antisera
- Successful DTT-treatment defined as destruction of K antigen and preservation of E antigen

Mitigation of Daratumumab Interference

ANTIBODY SCREENING

- Confirm Dara interference in IAT antibody screens (achieved in carryover study).
- Use Tube IAT method 15 minutes @37^{o}C with LISS using Dara plasma vs DTT-Treated Screencyte cells.
- Washed three times, tested using AHG.
- Macroscopically graded, negatives confirmed using IgG coated red cells
- Successful Mitigation- elimination of Dara Interference in DTT-IAT screen

CROSSMATCHING

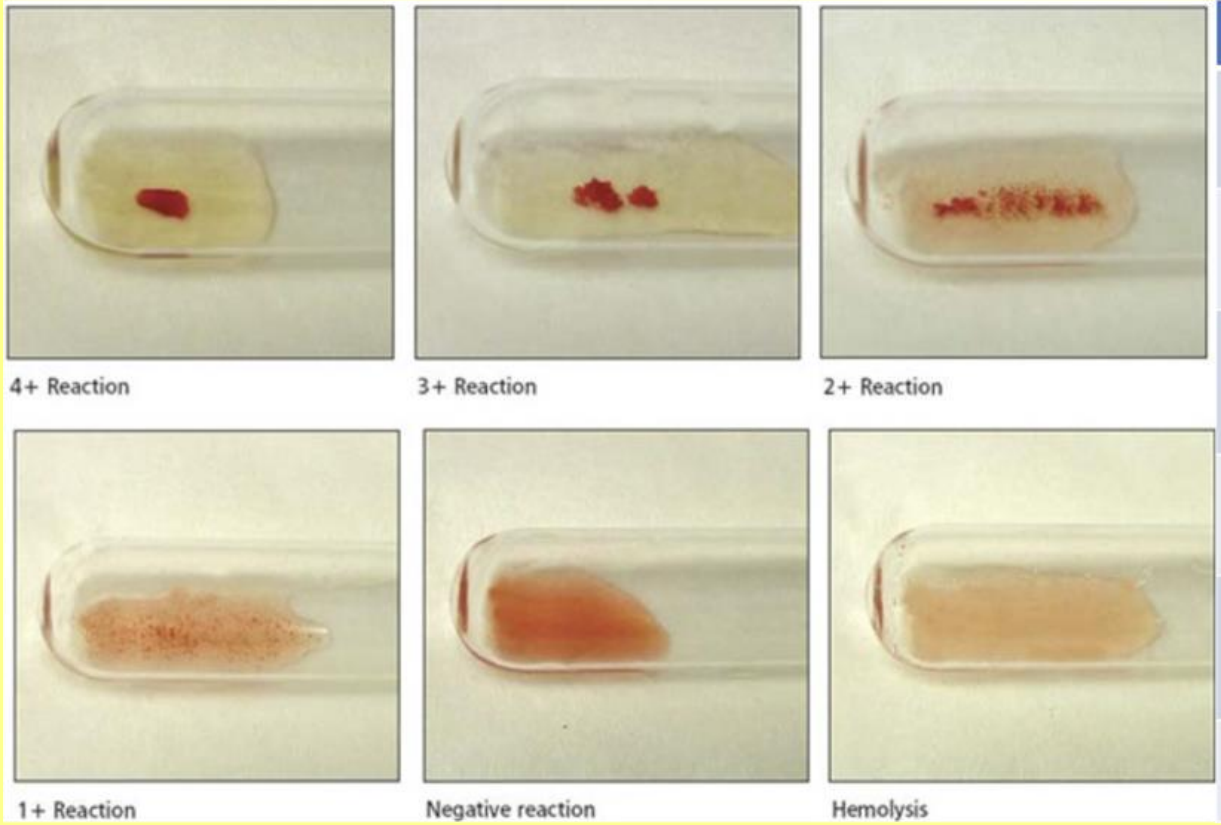
Confirm Dara interference in IAT crossmatching (achieved using Ortho vision Max) using ABO-compatible units.

- Tube IAT crossmatch 15 minutes @ 37^{o}C using DTT-treated donor unit red cells.
- Washed four times, tested using anti-IgG
- Macroscopically graded, negatives confirmed using IgG coated red cells
- Successful mitigation: Elimination of Dara interference in DTT-IAT screen.

Detection of underlying antibodies

- Assessment of ability of DTT-treated screening cells and Donor unit red cells to detect antibodies in DARA Plasma.
- Daratumumab plasma spiked with Reagent weak anti-D (0.99 IU/mL), Weak anti-c and weak anti-Fy^a (titre: 4).
- DARA samples with a titre of at least 512 diluted 1:1 with weak antisera yielding final strengths of 0.48 IU/mL (anti-D) or titres of 2 (weak anti-c and anti-Fy^a).
- Tested using tube-IAT antibody screens using DTT-treated screening cells and crossmatching using DTT-treated donor unit red cells with expression of corresponding antigen.
- Successful Detection: defined by removal of DARA interference and positive antibody screen and positive crossmatches with red cells possessing corresponding antigen.

Tube IAT Grading



Result	Grade
Absence of viable cells (Complete Haemolysis)	Haemolysis (Positive)
Single Large Agglutinate, No free Cells	4+
Multiple large Agglutinates, few free cells	3+
Small fine Agglutinates, some free cells	2+
Very small fine agglutinates, abundance of free cells	1+
No agglutinates, only free cells	Negative

Figure 7: macroscopic grading criteria for IAT tube invesitgations using DTT-treated cells.

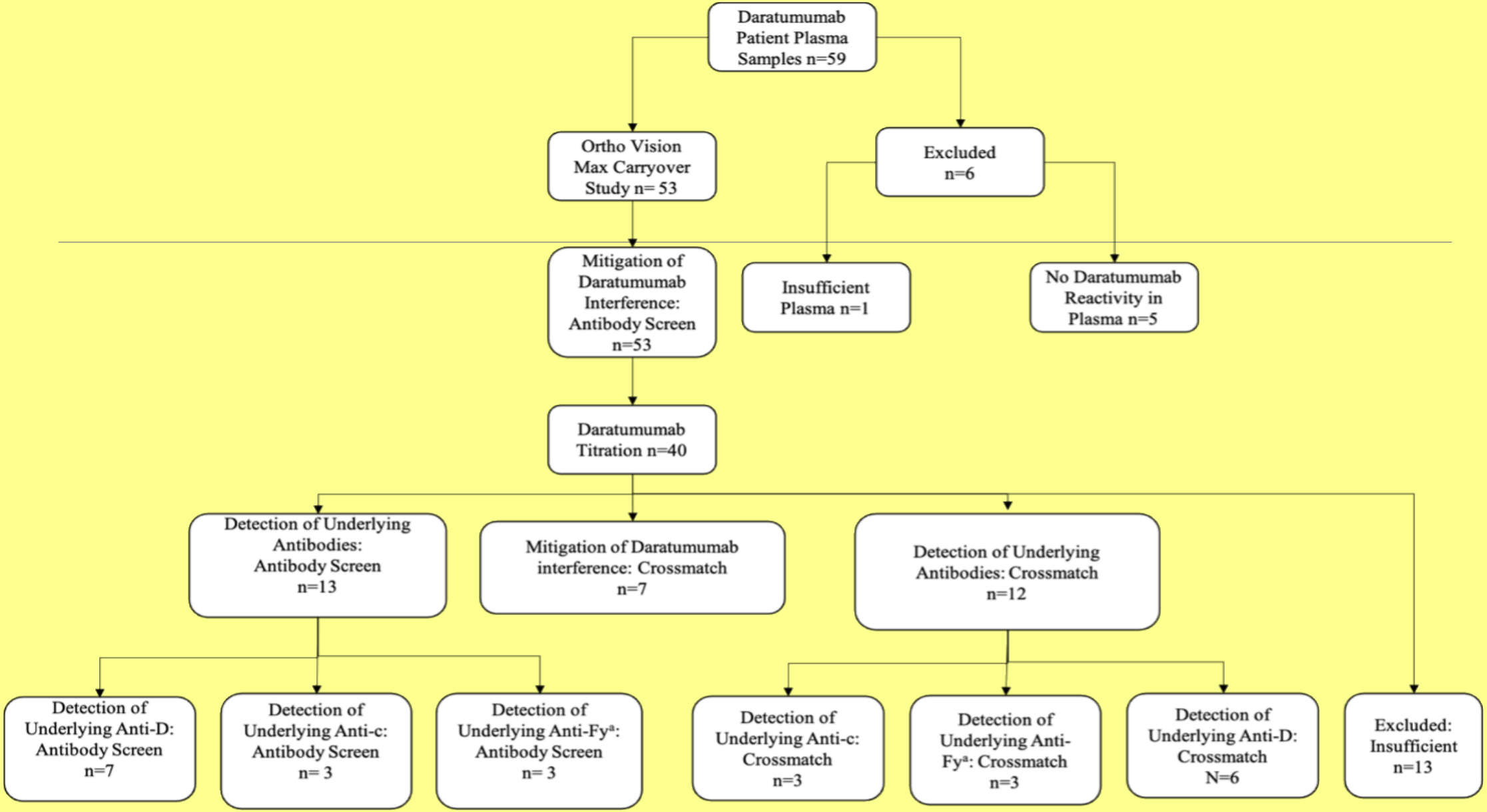


Figure 8: Breakdown of Samples used in all DARA investigations

Daratumumab Analyser Carryover Results

- 58 antibody screens performed, 5 samples Containing no Daratumumab.
- 2+ panreactivity Observed in majority of samples.
- No carryover observed in AB whole blood control when processed after any sample.
- DAT performed on Whole blood control cells after every 10th DARA sample.
- No carryover observed in any of the DATs performed

Table 1: Results of Daratumumab Analyser carryover study

IAT Antibody Screen Result			Frequency	Carryover
S1	S2	S3	n (%)	n (%)
2+	2+	2+	44 (75.9)	0 (0%)
2+	2+	1+	4 (6.9)	0 (0%)
1+	1+	1+	3(5.2)	0 (0%)
1+	w+	w+	1(1.7)	0 (0%)
w+	w+	w+	1(1.7)	0 (0%)
-	-	-	5 (8.6)	0 (0%)
		Total	58	0

Results of Daratumumab Quantitation

- Most common Dara titre observed was ≥1024 (57.5%)
- Limits of detection-could not distinguish between higher titres of Daratumumab.
- Relationship testing between Daratumumab titre and antibody screen test.
- Chi Square coefficient: 47.27 (p>0.001)
- Cramer's V Value: 0.628 (p>0.001)
- Strong association between Daratumumab titre and strength of Screen interference

Table 2: Titration results of 40 Daratumumab Samples

		Frequency (n)	Proportion (%)
Daratumumab Titre	1	1	2.5
	16	1	2.5
	32	2	5.0
	128	1	2.5
	256	3	7.5
	512	9	22.5
	≥1024	23	57.5
	Total	40	100.0

Results of Daratumumab Mitigation

- Four batches of screening cells and three donor units treated: all verified by loss or preservation of E of K antigens respectively.
- 53 antibody screens performed- complete mitigation of DARA interference regardless of initial IAT strength
- Seven Crossmatches performed using DTT-treated donor unit cells.
- Complete mitigation of DARA interference regardless of titre

Table 3: Results of Antibody screening and crossmatching using DTT-untreated and treated red cells

Antibody Screen Result			Pre-DTT Treatment n (%)	Post-DTT Treatment n (%)
S1	S2	S3		
2+	2+	2+	44 (83)	0
2+	2+	1+	4 (7.5)	0
1+	1+	1+	3(5.7)	0
1+	w+	w+	1(1.9)	0
w+	w+	w+	1(1.9)	0
-	-	-	0 (0)	53 (100)
		Total	53	

Patient Group	Daratumumab Titre	Unit Phenotype	CAT IAT Crossmatch (Pre-DTT treatment)	Tube IAT Crossmatch (post DTT Treatment)
O RhD positive	≥1024	O RhD positive Fy^{a}+	2+	Negative
O RhD positive	≥1024	O RhD positive c+	2+	Negative
O RhD positive	≥1024	O RhD positive Fya+	3+	Negative
O RhD positive	≥1024	O RhD positive c+	2+	Negative
A RhD negative	≥1024	O RhD positive Fy^{a}+	2+	Negative
A RhD negative	≥1024	A RhD negative c+	2+	Negative
A RhD positive	512	A RhD negative c+	1+	Negative

Detection of Underlying antibodies

- 13 antibody screens using antibody-spiked Dara plasma.
- Positive antibody screens observed in all Antibody screens.
- No Dara interference observed in any antibody screen.
- 12 crossmatches performed using Antisera-spiked Dara plasma and Antigen-positive DTT-treated.
- All 12 crossmatches positive-successful detection of all underlying antibodies.

Table 4: Detection of underlying antibodies in Daratumumab plasma via antibody screening and crossmatching using DTT-treated red cells

Spiked antibody	Number of samples tested (n)	Spiked Antibody activity (IU/ml)	Spiked Antibody Titre	Daratumumab Titre	Daratumumab Interference	Antibody Detected
Anti-D	6	<0.5	N/A	≥1024	Absent	Anti-D
Anti-D	1	<0.5	N/A	512	Absent	Anti-D
Anti-Fy^a	3	N/A	2	≥1024	Absent	Anti-Fy^a
Anti-c	3	N/A	2	≥1024	Absent	Anti-c

Spiked antibody	Number of samples tested (n)	Spiked Antibody activity (IU/m/)	Spiked Antibody Titre	Daratumumab Titre	Donor ABO group	Unit Phenotype	Crossmatch result
Anti-D	6	<0.5	≥1024	≥1024	O	RhD+	Positive
Anti-Fy^a	3	2	≥1024	≥1024	O	Fy^a +	Positive
Anti-c	3	2	≥1024	≥1024	O	c+	Positive

Key Findings

- Carryover of DARA into non-Dara samples on the Ortho Vision Max did not occur and was independent of strength of interference and antibody titre.
- The strength of DARA interference in IAT investigations is strongly related to the titre of Daratumumab in patient's samples
- Successful removal of CD38 and K antigens was achieved using DTT at pH 8.0.
- Complete mitigation of Daratumumab from 53 antibody screens and seven crossmatches was achieved using DTT treatment of red cells.
- Detection of underlying antibodies in Daratumumab plasma was achieved in 13 screens and 12 crossmatches.

Limitations

- Risk of carryover in samples with 3+/4+ DARA interference remains unknown- Interference of this strength is unlikely.
- Titration is not a conventional technique for DARA quantitation.
- Could not distinguish between titres of 1024 or greater.
- Shelf life of DTT-treated cells not investigated.
- Ability to detect, but not identify underlying antibodies assessed.

Implications for TUH

- Detection of underlying antibodies alone is likely to be sufficient for provision of blood components to Daratumumab patients in TUH.
- Financial cost reductions: €10.56 per in-house DTT-IAT crossmatch compared with €490.70 for referral testing. Estimated annual cost :€6,589.44 vs €306,196.80.
- Favourable Turnaround time: 2-4 Hours for In-house testing compared to approximately 24 hours
- British Society for Haematology : regents for Antibody screening should be CE marked where possible- no CE mark for DTT.
- No EQA scheme for DTT-IAT testing- Investigations outside of INAB scope.

Conclusion

- Daratumumab causes false positive IAT reactions and may mask underlying antibodies
- Change in Daratumumab indications for use may result in up to 15 patients per year receiving the monoclonal antibody therapy in TUH.
- Ortho Vision Max analyser is sufficient for Forward and reverse grouping of Dara patients due to minimal risk of carryover.
- DTT-treatment of screening cells and donor unit cells provides an inexpensive sensitive, reproducible means of screening and crossmatching patients receiving Daratumumab.

Reference List

- American Association of Blood Banking (2016) *Mitigating the Anti-CD38 Interference with Serologic Testing*.
- Anani, W. Q. *et al.* (2017) 'How do I work up pretransfusion samples containing anti-CD38?', *Transfusion*, 57(6), pp. 1337–1342. doi: 10.1111/trf.14144.
- Bashir, Q. *et al.* (2019) 'Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial', *The Lancet Haematology*, 6(5), pp. e266–e275. doi: 10.1016/S2352-3026(19)30023-7.
- Benboubker, L. *et al.* (2014) 'Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma', *New England Journal of Medicine*, 371(10), pp. 906–917. doi: 10.1056/nejmoa1402551.
- Bird, J. M. *et al.* (2011) 'Guidelines for the diagnosis and management of multiple myeloma 2011', *British Journal of Haematology*, 154(1), pp. 32–75. doi: 10.1111/j.1365-2141.2011.08573.x.
- Birgegård, G., Gascón, P. and Ludwig, H. (2006) 'Evaluation of anaemia in patients with multiple myeloma and lymphoma: Findings of the European Cancer Anaemia Survey', *European Journal of Haematology*, 77(5), pp. 378–386. doi: 10.1111/j.1600-0609.2006.00739.x.
- BSH (2017) *Managing patients who are being treated with targeted therapeutic monoclonal antibodies.*
- Bub, C. B. *et al.* (2018) 'Transfusion management for patients taking an anti-CD38 monoclonal antibody', *Hematology, Transfusion and Cell Therapy*, 40(1), pp. 25–29. doi: 10.1016/j.bjhh.2017.09.003.
- Burwick, N. (2018) 'Glucocorticoids in multiple myeloma : past , present , and future', *Annals of Hematology*, pp. 19–28.
- Castaneda, O. and Baz, R. (2019) 'Multiple Myeloma Genomics - A Concise Review', *Acta medica academica*, 48(1), pp. 57–67. doi: 10.5644/ama2006-124.242.
- Chapuy, C. I. *et al.* (2015) 'Resolving the daratumumab interference with blood compatibility testing', *Transfusion*, 55(6), pp. 1545–1554. doi: 10.1111/trf.13069.
- Chapuy, C. I. *et al.* (2016) 'International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing', *Transfusion*, 56(12), pp. 2964–2972. doi: 10.1111/trf.13789.
- Chari, A. *et al.* (2015) 'Outcomes and Management of Red Blood Cell Transfusions in Multiple Myeloma Patients Treated with Daratumumab', *Blood*, 126(23), pp. 3571–3571. doi: 10.1182/blood.v126.23.3571.3571.
- Chini, E. (2009) 'CD38 as a Regulator of Cellular NAD: A Novel Potential Pharmacological Target for Metabolic Conditions', *Current Pharmaceutical Design*, 15(1), pp. 57–63. doi: 10.2174/138161209787185788.
- Chung, H. J. *et al.* (2019) 'Benefits of VISION max automated crossmatching in comparison with manual crossmatching: A multidimensional analysis', *PLoS ONE*, 14(12), pp. 1–13. doi: 10.1371/journal.pone.0226477.
- Clemens, P. L. *et al.* (2017) 'Pharmacokinetics of Daratumumab Following Intravenous Infusion in Relapsed or Refractory Multiple Myeloma After Prior Proteasome Inhibitor and Immunomodulatory Drug Treatment', *Clinical Pharmacokinetics*, 56(8), pp. 915–924. doi: 10.1007/s40262-016-0477-1.
- Deneys, V. *et al.* (2018) 'Daratumumab: Therapeutic asset, biological trap!', *Transfusion Clinique et Biologique*, 25(1), pp. 2–7. doi: 10.1016/j.tracli.2017.12.001.
- Dimopoulos, M. A. *et al.* (2018) 'Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial', *Cancer*, 124(20), pp. 4032–4043. doi: 10.1002/cncr.31680.
- Emery, V. *et al.* (2013) 'Management of cytomegalovirus infection in haemopoietic stem cell transplantation', *British Journal of Haematology*, 162(1), pp. 25–39. doi: 10.1111/bjh.12363.
- European Commission (2004) *Guidelines on Medical Devices MEDDEV 2.14/2 rev 1, IVD GUIDANCE : Research Use Only products*.
- European Commission (2012) *IVD Medical Device Borderline and Classification issues : A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES*.
- European Medicines Agency (2016) 'Darzalex (daratumumab) - Assessment report', *European Medicine Agency Science Medicines Health*, 44(April), p. 119.
- Fan, L. *et al.* (2017) 'Prognostic Significance of Blood Transfusion in Newly Diagnosed Multiple Myeloma Patients without Autologous Hematopoietic Stem Cell Transplantation'. doi: 10.1155/2017/5462087.
- Feng, X. *et al.* (2017) 'Targeting CD38 suppresses induction and function of T regulatory cells to mitigate immunosuppression in multiple myeloma', *Clinical cancer research : an official journal of the American Association for Cancer Research*, 23(15), pp. 4290–4300. doi: 10.1158/1078-0432.CCR-16-3192.Targeting.
- Ferlay, J. *et al.* (2018) 'Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018', *European Journal of Cancer*, 103, pp. 356–387. doi: 10.1016/j.ejca.2018.07.005.
- Fink, E. C. and Ebert, B. L. (2015) 'The novel mechanism of lenalidomide activity', *Blood*, pp. 2366–2369. doi: 10.1182/blood-2015-07-567958.

Reference List continued

- Foukaneli, T. *et al.* (2020) 'Guidelines on the use of irradiated blood components', *British Journal of Haematology*, (October), pp. 1–21. doi: 10.1111/bjh.17015.
- Furukawa, Y. and Kikuchi, J. (2015) 'Molecular pathogenesis of multiple myeloma', *International Journal of Clinical Oncology*, 20(3), pp. 413–422. doi: 10.1007/s10147-015-0837-0.
- Gavriatopoulou, M. *et al.* (2017) 'Efficacy and safety of elotuzumab for the treatment of multiple myeloma', *Expert Opinion on Drug Safety*, 16(2), pp. 237–245. doi: 10.1080/14740338.2017.1279603.
- Ghose, J. *et al.* (2018) 'Daratumumab induces CD38 internalization and impairs myeloma cell adhesion', *OncoImmunology*, 7(10), pp. 1–11. doi: 10.1080/2162402X.2018.1486948.
- Hall, H. (2016) 'Practical Blood Bank Lab 7 Antibody Identification Antibody', in. Available at: https://slidetodoc.com/practical-blood-bank-lab-7-antibody-identification-antibody/ (Accessed: 4 April 2021).
- Hou, J. *et al.* (2019) 'The impact of the bone marrow microenvironment on multiple myeloma (Review)', *Oncology Reports*, 42(4), pp. 1272–1282. doi: 10.3892/or.2019.7261.
- Hulin, C. *et al.* (2019) 'Bortezomib retreatment for relapsed and refractory multiple myeloma in real-world clinical practice', *Health Science Reports*, 2(1), pp. 1–11. doi: 10.1002/hsr2.104.
- Izaguirre, E. C. *et al.* (2020) 'New method for overcoming the interference produced by anti-CD38 monoclonal antibodies in compatibility testing', *Blood Transfusion*, 18(4), pp. 290–294. doi: 10.2450/2020.0004-20.
- Jagannath, S. *et al.* (2004) 'A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma', *British Journal of Haematology*, 127(2), pp. 165–172. doi: 10.1111/j.1365-2141.2004.05188.x.
- Janssen (2017) *DARZALEX ®. Daratumumab. Product Information*, *JANSSEN-CILAG Pty Ltd*. Available at: http://www.janssen.com/australia/sites/www_janssen_com_australia/files/prod_files/live/darzalex_pi.pdf.
- Janssen Biotech Inc. (2015) *Darzlaex Prescribing Information*. Horsham, PA. Available at: www.fda.gov/medwatch. (Accessed: 27 February 2021).
- Janssen Biotech Inc (2020) *Daratumumab Prescribing Information*. Horsham, PA. Available at: www.fda.gov/medwatch. (Accessed: 27 February 2021).
- Kervoëlen, C. *et al.* (2015) 'Dexamethasone-induced cell death is restricted to specific molecular subgroups of multiple myeloma', *Oncotarget*, 6(29), pp. 26922–26934. doi: 10.18632/oncotarget.4616.
- Kim, Y. and Schmidt-Wolf, I. G. (2015) 'Lenalidomide in multiple myeloma', *Expert Review of Anticancer Therapy*, 15(5), pp. 491–497. doi: 10.1586/14737140.2015.1033407.
- Krejcik, J. *et al.* (2016) 'Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma', *Blood*, pp. 384–394. doi: 10.1182/blood-2015-12-687749.
- Lancman, G. *et al.* (2018) 'Blood Transfusion Management for Patients Treated With Anti-CD38 Monoclonal Antibodies', *Frontiers in Immunology*, 9(NOV), p. 2616. doi: 10.3389/fimmu.2018.02616.
- Lee, H. C. (2006) 'Structure and enzymatic functions of human CD38', in *Molecular Medicine*, pp. 317–323. doi: 10.2119/2006-00086.Lee.
- Lin, M. H. *et al.* (2017) 'Interference of daratumumab with pretransfusion testing, mimicking a high-titer, low avidity like antibody', *Asian Journal of Transfusion Science*, 11(2), pp. 209–211. doi: 10.4103/0973-6247.214358.
- Lintel, N. J. *et al.* (2017) 'Use of standard laboratory methods to obviate routine dithiothreitol treatment of blood samples with daratumumab interference', *Immunohematology*, 33(1), pp. 22–26.
- Liu, L. *et al.* (2020) 'Multiple myeloma hinders erythropoiesis and causes anaemia owing to high levels of CCL3 in the bone marrow microenvironment', *Scientific Reports*, 10(1), pp. 1–14. doi: 10.1038/s41598-020-77450-y.
- Liu, Q. *et al.* (2005) 'Crystal structure of human CD38 extracellular domain', *Structure*, 13(9), pp. 1331–1339. doi: 10.1016/j.str.2005.05.012.
- Lokhorst, H. M. *et al.* (2015) 'Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma', *New England Journal of Medicine*, 373(13), pp. 1207–1219. doi: 10.1056/nejmoa1506348.
- Long, J., Doyle, B. and Niloingsigh, S. (2016) *Mitigating Daratumumab Interference in the Laboratory*.
- Lonial, S. *et al.* (2016) 'Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): An open-label, randomised, phase 2 trial', *The Lancet*, 387(10027), pp. 1551–1560. doi: 10.1016/S0140-6736(15)01120-4.
- Lonial, S. *et al.* (2020) 'Randomized trial of lenalidomide versus observation in smoldering multiple myeloma', *Journal of Clinical Oncology*, 38(11), pp. 1126–1137. doi: 10.1200/JCO.19.01740.
- Mateos, M.-V. *et al.* (2013) 'Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma', *New England Journal of Medicine*, 369(5), pp. 438–447. doi: 10.1056/nejmoa1300439.
- Mateos, M.-V. *et al.* (2020) 'Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial', *The Lancet*, 395(10218), pp. 132–141. doi: 10.1016/S0140-6736(19)32956-3.
- Miguel, J. S. *et al.* (2013) 'Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial', *The Lancet Oncology*, 14(11), pp. 1055–1066. doi: 10.1016/S1470-2045(13)70380-2.
- Milkins, C. *et al.* (2013) 'Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories', *Transfusion Medicine*, 23(1), pp. 3–35. doi: 10.1111/j.1365-3148.2012.01199.x.
- Morandi, F. *et al.* (2018) 'CD38: A Target for Immunotherapeutic Approaches in Multiple Myeloma', *Frontiers in Immunology*, 9, p. 2722. doi: 10.3389/FIMMU.2018.02722.

Reference List

- Nakamura, F. and Nasu, R. (2019) 'Prolonged severe neutropenia after the first daratumumab administration for multiple myeloma with baseline neutropenia', *Annals of Hematology*, 98(9), pp. 2231–2232. doi: 10.1007/s00277-019-03711-0.
- van Nieuwenhuijzen, N. *et al.* (2018) 'From MGUS to multiple myeloma, a paradigm for clonal evolution of premalignant cells', *Cancer Research*, 78(10), pp. 2449–2456. doi: 10.1158/0008-5472.CAN-17-3115.
- Nijhof, I. S. *et al.* (2016) 'CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma', *Blood*, 128(7), pp. 959–970. doi: 10.1182/blood-2016-03-703439.
- Oostendorp, M., Lammerts Van Bueren, J. J., *et al.* (2015) 'When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy', *Transfusion*, 55(6), pp. 1555–1562. doi: 10.1111/trf.13150.
- Oostendorp, M., Lammerts van Bueren, J. J., *et al.* (2015) 'When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy', *Transfusion*, 55(6pt2), pp. 1555–1562. doi: 10.1111/trf.13150.
- Ortho Clinical Diagnostics (2020) *URGENT FIELD SAFTEY NOTICE Potential Intermittent False Positives on ORTHO VISION and ORTHO VISION Max BioVue Analyzers When Testing High Titer Samples*. Available at: https://www.hpra.ie/docs/default-source/field-safety-notices/august-2020/v44591_fsn.pdf?sfvrsn=2.
- Overdijk, M. B. *et al.* (2015) 'Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma', *mAbs*, 7(2), pp. 311–320. doi: 10.1080/19420862.2015.1007813.
- Overdijk, M. B. *et al.* (2016) 'The Therapeutic CD38 Monoclonal Antibody Daratumumab Induces Programmed Cell Death via Fcγ Receptor–Mediated Cross-Linking', *The Journal of Immunology*, 197(3), pp. 807–813. doi: 10.4049/jimmunol.1501351.
- Pandey, P. *et al.* (2020) 'Blood component administration to multiple myeloma patients treated with daratumumab: suggesting a novel approach with use of 0.1 M dithiothreitol', *Immunohematology*, 36(4), pp. 157–165.
- Rajkumar, S. V. (2020) 'Multiple myeloma: 2020 update on diagnosis, risk-stratification and management', *American Journal of Hematology*, 95(5), pp. 548–567. doi: 10.1002/ajh.25791.
- Roback JD, Grossman BJ, Harris T, H. C. and Smith, J. (2019) *Technical Manual of the American Assoc of Blood Banks.*, *Technical Manual of the American Assoc of Blood Banks.* Available at: https://www.amazon.com/Technical-Manual-American-Assoc-Blood/dp/1563958880?SubscriptionId=AKIAIOBINVZYXZQZ2U3A&tag=chimbori05-20&linkCode=xm2&camp=2025&creative=165953&creativeASIN=1563958880.
- Robak, P. and Robak, T. (2019) 'Bortezomib for the Treatment of Hematologic Malignancies: 15 Years Later', *Drugs in R and D*, 19(2), pp. 73–92. doi: 10.1007/s40268-019-0269-9.
- Scott, K. *et al.* (2016) 'Bortezomib for the treatment of multiple myeloma', *Cochrane Database of Systematic Reviews*, 2016(4). doi: 10.1002/14651858.CD010816.pub2.
- Selleng, K., Gebicka, P. D. and Thiele, T. (2018) ' F(ab') 2 Fragments to Overcome Daratumumab Interference in Transfusion Tests ', *New England Journal of Medicine*, 379(1), pp. 90–91. doi: 10.1056/nejmc1804751.
- Sergentanis, T. N. *et al.* (2015) 'Risk Factors for Multiple Myeloma: A Systematic Review of Meta-Analyses', *Clinical Lymphoma, Myeloma and Leukemia*, 15(10), pp. 563-577.e3. doi: 10.1016/j.clml.2015.06.003.
- Sigle, J. P. *et al.* (2018) 'Extending shelf life of dithiothreitol-treated panel RBCs to 28 days', *Vox Sanguinis*, 113(4), pp. 397–399. doi: 10.1111/vox.12645.
- Sullivan, H. C. *et al.* (2017) 'Daratumumab (anti-CD38) induces loss of CD38 on red blood cells', *Blood*, pp. 3033–3037. doi: 10.1182/blood-2016-11-749432.
- Tomlinson, T. (2018) 'Antibody Investigation', in. London. Available at: https://www.transfusionguidelines.org/document-library/documents/antibody-investigation-t-tomlinson-pdf/download-file/Antibody investigation T Tomlinson.pdf.
- Tsang, M. *et al.* (2019) 'Multiple myeloma epidemiology and patient geographic distribution in Canada: A population study', *Cancer*, 125(14), pp. 2435–2444. doi: 10.1002/cncr.32128.
- de Weers, M. *et al.* (2011) 'Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors', *The Journal of Immunology*, 186(3), pp. 1840–1848. doi: 10.4049/jimmunol.1003032.
- Werle, E. *et al.* (2019) 'Daratumumab Interference in Pretransfusion Testing Is Overcome by Addition of Daratumumab Fab Fragments to Patients' Plasma', *Transfusion Medicine and Hemotherapy*, 46(6), p. 423. doi: 10.1159/000495773.
- Ye, Z. *et al.* (2020) 'Risk of RBC alloimmunization in multiple myeloma patients treated by Daratumumab', *Vox Sanguinis*, 115(2), pp. 207–212. doi: 10.1111/vox.12864.
- Youssef, M. *et al.* (2019) 'Validation and cost-effectiveness of an in-house dithiothreitol (DTT)treatment protocol for daratumumab patients in a large tertiary care hospital provides gateway for implementation in smaller community hospitals', *Transfusion and Apheresis Science*, 58(2), pp. 152–155. doi: 10.1016/j.transci.2018.12.019.
- Zhang, T. *et al.* (2017) 'Systematic review and meta-analysis of the efficacy and safety of novel monoclonal antibodies for treatment of relapsed/ refractory multiple myeloma', *Oncotarget*, 8(20), pp. 34001–34017. doi: 10.18632/oncotarget.16987.