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THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.27 NO.12 December 2022

Haematology

OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

EVENITY®
(romosozumab) injection

prolia®
(denosumab)

Every patient has a different starting point

MEET HER THERE

and help make her bones stronger

For your patients with **very low T-score** (e.g. less than -3.0) or with other serious risk factors, start with **EVENITY®** followed by **PROLIA®** to help build and protect her bones.[1]

For your partients **with history of fragility fracture or low T-score** (e.g. less than -2.5) with other risk factors, start with **PROLIA®** to help strengthen her bones.[2,3]

* The risk of hip fracture was lowered by 38% (41 of 2046 patients [2.0%] vs. 66 of 2047 patients [3.2%]; P = 0.02) in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group in ARCH Study.[1]

† Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk. Patients who have been diagnosed with osteoporosis but are not at very high fracture risk are defined as high risk.[3]

ARCH=Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BMD=Bone mineral density.

References: 1. Evenity (romosozumab) Hong Kong prescribing information. March 2020. **2.** Prolia (denosumab) Hong Kong prescribing information. Aug 2020. **3.** Camacho PM, et al. Endocr Pract. 2020;26(Suppl 1).

Prolia® (Denosumab) Abbreviated Prescribing Information
Prolia® (denosumab) Solution for Injection in Pre-filled Syringe 60 mg/mL

INDICATIONS Prolia is indicated for: i) treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; ii) treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; iii) treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy; iv) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures; v) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. **DOSAGE AND ADMINISTRATION** The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily. **CONTRAINDICATIONS** Hypocalcemia and pregnancy, as well as hypersensitivity to any component of the product. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Hypersensitivity: Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritis, and urticaria. Hypocalcemia and Mineral Metabolism: Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. Concomitant use of calcimimetic drugs may worsen hypocalcemia risk and serum calcium should be closely monitored. Adequately supplement all patients with calcium and vitamin D. Osteonecrosis of the Jaw (ONJ): ONJ has been reported in patients receiving Prolia. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Prolia. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to Prolia treatment. Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia. Patients should be advised to report new or unusual thigh, hip, or groin pain. Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment: Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. If Prolia treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy. Serious Infections: Serious infections leading to hospitalization were reported in clinical trial. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. Dermatologic Adverse Reactions: Dermatitis, eczema, and rashes. Most of these events were not specific to the injection site. Consider discontinuing Prolia if severe symptoms develop. Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain. Consider discontinuing use if severe symptoms develop. Suppression of Bone Turnover: In clinical trials treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. Osteonecrosis of the external auditory canal: Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. **PREGNANCY AND LACTATION** Pregnancy: Contraindicated. Breast-feeding: No information regarding the presence of denosumab in human milk, the effects on the breastfed infant, or the effects on milk production **PEDIATRIC, GERIATRIC AND RENAL IMPAIRMENT** Pediatric: Prolia is not recommended in pediatric patients younger than age 4 years. Geriatric: No overall differences in safety or efficacy were observed in clinical studies between elderly patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Renal Impairment: No dose adjustment is necessary in patients with renal impairment. **UNDESIRABLE EFFECTS** The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. The most common adverse reactions reported with Prolia in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache. The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation. **OVERDOSE** There is no experience with overdosage with Prolia.

Abbreviated Prescribing Information Version: HKPROPI02

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Prolia® is a registered trademark owned or licensed by Amgen Inc., its subsidiaries, or affiliates.

EVENITY® (Romosozumab) Abbreviated Prescribing Information
EVENITY® Solution for Injection in Prefilled Syringe 105 mg/1.17 ml

INDICATIONS EVENITY is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture. **DOSAGE AND ADMINISTRATION** The recommended dose is 210 mg romosozumab (administered as two subcutaneous injections of 105 mg each) once monthly for 12 months. Patients should be adequately supplemented with calcium and vitamin D before and during treatment. Following completion of romosozumab therapy, transition to antiresorptive therapy is recommended in order to extend the benefit achieved with romosozumab beyond 12 months. Missed doses: If the romosozumab dose is missed, administer as soon as it can be feasible. Thereafter, the next romosozumab dose should not be given earlier than one month after the last dose. Elderly: No dose adjustment is necessary in elderly patients. Renal impairment: No dose adjustment is required in patients with renal impairment. Serum calcium should be monitored in patients with severe renal impairment or receiving dialysis. Hepatic impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment. Paediatric population: The safety and efficacy of romosozumab in paediatric patients (age <18 years) have not yet been established. No data are available. Method of administration: Subcutaneous use. To administer the 210 mg dose, 2 subcutaneous injections of romosozumab should be given into the abdomen, thigh, or upper arm. The second injection should be given immediately after the first one but at a different injection site. Administration should be performed by an individual who has been trained in injection techniques. **CONTRAINDICATIONS** Hypersensitivity to the active substance(s) or to any of the excipients. Hypocalcaemia. History of myocardial infarction or stroke. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Myocardial infarction and stroke: In randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls. When determining whether to use romosozumab for an individual patient, consideration should be given to her fracture risk over the next year and her cardiovascular risk based on risk factors (e.g. established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). Romosozumab should only be used if the prescriber and patient agree that the benefit outweighs the risk. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued. Hypocalcaemia: Transient hypocalcaemia has been observed in patients receiving romosozumab. Hypocalcaemia should be corrected prior to initiating therapy with romosozumab and patients should be monitored for signs and symptoms of hypocalcaemia. If any patient presents with suspected symptoms of hypocalcaemia during treatment, calcium levels should be measured. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 ml/min/1.73 m2) or receiving dialysis are at greater risk of developing hypocalcaemia and the safety data for these patients is limited. Calcium levels should be monitored in these patients. Hypersensitivity: Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria occurred in the romosozumab group in clinical trials. If an anaphylactic or other clinically significant allergic reaction occurs, appropriate therapy should be initiated and use of romosozumab should be discontinued. Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ), has been reported rarely in patients receiving romosozumab. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with romosozumab. Patients who are suspected of having or who develop ONJ while on romosozumab should receive care by a dentist or an oral surgeon with expertise in ONJ. Discontinuation of romosozumab therapy should be considered until the condition resolves and contributing risk factors are mitigated where possible. Atypical femoral fractures: Atypical low-energy or low trauma fracture of the femoral shaft, which can occur spontaneously, has been reported rarely in patients receiving romosozumab. Any patient who presents with new or unusual thigh, hip, or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of romosozumab therapy should be considered, based on an individual benefit-risk assessment. Sodium content: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free. **INTERACTIONS** No drug interaction studies have been performed with romosozumab. No pharmacokinetic drug interactions are expected with romosozumab. **PREGNANCY AND LACTATION** Pregnancy: Romosozumab is not indicated for use in women of child-bearing potential or in pregnant women. There are no data from the use of romosozumab in pregnant women. A risk for malformations of developing digits in the human foetus is low following romosozumab exposure due to the timing of digit formation in the first trimester in humans, a period when placental transfer of immunoglobulins is limited. Breast-feeding: Romosozumab is not indicated for use in breast-feeding women. No data are available on excretion of romosozumab in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Fertility: No data are available on the effect of romosozumab on human fertility. Animal studies in female and male rats did not show any effects on fertility endpoints. **ADVERSE REACTIONS** The most common adverse reactions were nasopharyngitis (15.6%) and arthralgia (12.4%). Hypersensitivity-related reactions occurred in 6.7% of patients treated with romosozumab. Hypocalcaemia was reported uncommonly (0.4% of patients treated with romosozumab). In randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls. Adverse reactions are presented in order of decreasing seriousness by System Organ Class: *Infections and infestations*: Nasopharyngitis, Sinusitis; *Immune system disorders*: Hypersensitivity, Rash, Dermatitis, Urticaria, Angioedema, Erythema multiforme; *Metabolism and nutrition disorders*: Hypocalcaemia; *Nervous system disorders*: Headache, Stroke; *Eye disorders*: Cataract; *Cardiac disorders*: Myocardial infarction; *Musculoskeletal and connective tissue disorders*: Arthralgia, Neck pain, Muscle spasms; *General disorders and administration site conditions*: Injection site reactions **OVERDOSE** There is no experience with overdose in clinical trials.

Abbreviated Prescribing Information Version No.: HKEVEPI01

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HK-08946-EVE-2022-Sep

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The Cover Shot

A Sunset Scene in Hong Kong.

In the months of October and November, numerous locals and visitors gather at Tsuen Wan West seaside to watch the awesome scenes of sunset over Ting Kau Bridge. In fine weather, the golden sun sets behind the bridge creating intriguing silhouettes of the bridge cables, traffic vehicles, and incoming flights intersecting its set path.

This cover photo captured an image of the glamorous setting sun, silhouettes of heavy traffic and an inbound flight which together conjured up a gratifying scene attesting to the return of prosperity to Hong Kong after three long years of hardship under the Covid pandemic.

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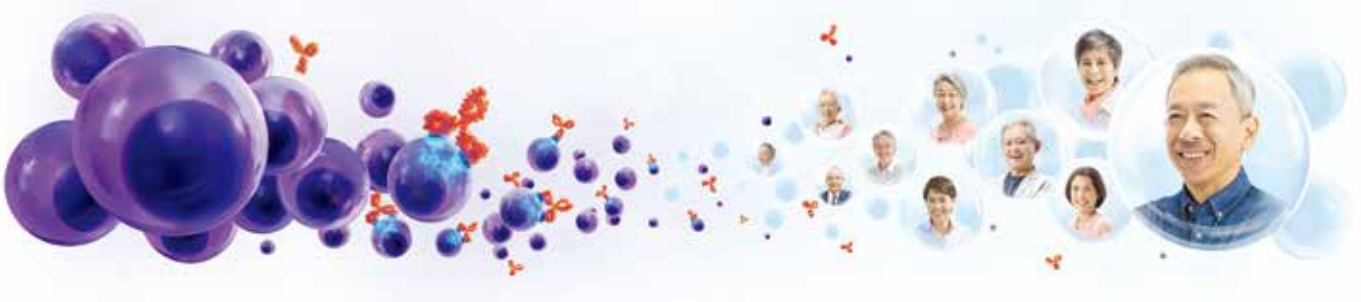
Dr Albert YF KONG, MH
MBBS, FRCPCH, FRCP(Edin.& Glasg.), FRACGP, FHKCPaed, FHKCFP, DCH, DPD, DFM, FHKAM(Paed)
Specialist in Paediatrics
Council Member,
Hong Kong Chinese Medical Association

IN THE TREATMENT OF **RELAPSED REFRACTORY MULTIPLE MYELOMA**

SARCLISA® (isatuximab)

ACHIEVE **GREATER OUTCOMES** FOR **YOUR PATIENTS**



IKEMA[2,4]: SARCLISA + Kd vs Kd (N=302)

mPFS 35.7 mo*
vs 19.2 mo with Kd alone

HR=0.58
(95.4% CI: 0.42–0.79)

Superior PFS[1]

ICARIA[3]: SARCLISA + Pd vs Pd (N=307)

mPFS 11.53 mo
vs 6.47 mo with Pd alone

HR=0.596
(95% CI: 0.44–0.81; *P*=0.001)

IKEMA trial: SARCLISA + Kd[1,2]

IKEMA (EFC15246) was a multicentre, multinational, randomised, open-label, 2-arm, phase 3 study that evaluated the efficacy and safety of SARCLISA in 302 patients with relapsed and/or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Kd (n=179) or Kd alone (n=123), administered in 28-day cycles until disease progression or unacceptable toxicity. PFS was the primary endpoint; secondary endpoints included ORR, CR, ≥VGPR, MRD-, and OS. Median follow-up for the first interim analysis was 20.7 months.

ICARIA trial: SARCLISA + Pd[1,3]

ICARIA (EFC14335) was a multicentre, multinational, randomised, open-label, 2-arm, phase 3 study that evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed and refractory multiple myeloma who had received at least 2 prior lines of therapy, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. PFS was the primary endpoint; ORR was one of the secondary endpoints. Median follow-up for the first interim analysis was 11.6 months.

Most common adverse reactions[1,2,4]

- In ICARIA, the most frequent adverse reactions (≥20%) were neutropenia (47%), infusion reactions (38%), pneumonia (31%), upper respiratory tract infection (28%), diarrhoea (26%), and bronchitis (24%)
- In IKEMA, the most frequent adverse reactions (≥20%) were infusion reactions (46%), hypertension (37%), diarrhoea (36%), upper respiratory tract infection (36%), pneumonia (29%), fatigue (28%), dyspnoea (28%), insomnia (24%), bronchitis (23%), and back pain (22%).

SARCLISA is indicated:

- In combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy
- In combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

*Assessment by masked independent response committee (IRC)

References: 1. Sarclisa Hong Kong prescribing information based on EU SmPC 29 July 2021. 2. Moreau P, et al. Lancet 2021; 397: 2361–71. 3. Attal M, et al. Lancet. 2019;394(10214):2096-2107. 4. Moreau P, et al. Presented at ESMO Virtual Plenaries, 2022 and 8th COMy World Congress. 20th May, 2022.

Presentation: SARCLISA 20 mg/mL concentrate for solution for infusion. One ml of concentrate for solution for infusion contains 20 mg of isatuximab. Each vial contains 100 mg of isatuximab in 5 mL of concentrate (100 mg/5mL). Each vial contains 500 mg of isatuximab in 25 mL of concentrate (500 mg/25mL). Indications: I. In combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. II. In combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Dosage & Administration: Intravenous infusion. Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

Cycles	Dosing schedule
Cycle 1	Days 1, 8, 15, and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

Premedication should be used prior to SARCLISA infusion with the following medicinal products: I. a. Dexamethasone 40 mg oral or intravenous (or 20 mg oral or intravenous for patients≥75 years of age): when administered in combination with isatuximab and pomalidomide. b. Dexamethasone 20 mg (intravenous on the days of isatuximab and/or Carfilzomib infusions, and oral on the other days): when administered in combination with isatuximab and carfilzomib. II. Acetaminophen 650 mg to 1000 mg oral (or equivalent). III. Diphenhydramine 25 mg to 50 mg intravenous or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous route is preferred for at least the first 4 infusions. The above recommended dose of dexamethasone corresponds to the total dose to be administered only once before the infusion. The recommended premedication agents should be administered 15-60 minutes prior to starting a SARCLISA infusion. Contraindications: Hypersensitivity to the active substance or to any of its excipients. Precautions: Vital signs should be frequently monitored during the entire SARCLISA infusion. When required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures. In case symptoms do not improve to grade≤3 after interruption of SARCLISA infusion, persist or worsen despite appropriate medicinal products, require hospitalization or are life-threatening, permanently discontinue SARCLISA and institute appropriate management. Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. No dose reductions of SARCLISA are recommended. SARCLISA dose delays and the use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted. Antibiotics and antiviral prophylaxis can be considered during treatment. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated. To avoid potential problems with RBC transfusion, patients being treated with SARCLISA should have blood type and screen tests performed prior to the first infusion. Phenotyping may be considered prior to starting SARCLISA treatment as per local practice. If treatment with SARCLISA has already started, the blood bank should be informed. Patients should be monitored for theoretical risk of haemolysis. If an emergency transfusion is required, non-cross-matched ABO/Rh-compatible RBCs can be given as per local blood bank practices. Drug Interactions: Isatuximab has no impact on the pharmacokinetics of pomalidomide or carfilzomib, or vice versa. Pregnancy and lactation: There are no available data on isatuximab use in pregnant women. Animal reproduction toxicity studies have not been conducted with isatuximab. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of isatuximab in pregnant women is not recommended. It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed child cannot be excluded during this short period just after birth. For this specific period, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Afterwards, isatuximab could be used during breast-feeding if clinically needed. Undesirable effects: isatuximab in combination with pomalidomide and dexamethasone: Most common adverse reactions reported- pneumonia, upper respiratory tract infection, bronchitis, neutropenia, febrile neutropenia, dyspnoea, diarrhoea, nausea, vomiting, infusion reaction. isatuximab in combination with carfilzomib and dexamethasone: Most common adverse reaction reported- pneumonia, upper respiratory tract infection, bronchitis, hypertension, dyspnoea, cough, diarrhoea, vomiting, fatigue, infusion reaction. For other undesirable effects, please refer to the full prescribing information. Preparation: The preparation of the infusion solution must be done under aseptic conditions. Legal Classification: Part 1, First & Third Schedules Poison Full prescribing information is available upon request.

API-HK-SAR-22.01

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MAT-HK-2200190-1.0-06/2022 4iC_2269

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

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Editor

Prof Eric Wai-choi TSE

Therapeutic approaches for cancers have evolved in the past two decades, and many novel anti-cancer treatment modalities are highly effective and have excellent safety profiles. Among them, immunotherapy is increasingly being used for the treatment of many different cancers, including haematological malignancies. The term "cancer immunotherapy" can be broadly defined as treatment that harnesses the anti-cancer activities of the immune system to kill neoplastic cells. In this issue of the Hong Kong Medical Diary, various forms of immunotherapy for the treatment of haematological malignancies are discussed.

By unleashing the inhibition exerted by neoplastic cells and tumour micro-environment on the body's immune surveillance, immune checkpoint blockade therapy restores the anti-cancer activities of patients' own T-cells. In his article, Prof Kwong Yok-lam has discussed the use of immune checkpoint blockade therapies in haematological malignancies, including classical Hodgkin lymphoma and NK/T-cell lymphoma.

Monoclonal antibodies targeting specific cancer surface antigens are incorporated into the therapeutic regimens for different haematological malignancies. The anti-CD20 antibody rituximab is the prototype and is used for the treatment of almost all B-cell neoplasms. In addition to "naked" monoclonal antibodies, antibody-drug conjugates and bispecific antibody T-cell engagers are armamentaria used to improve the treatment outcomes of patients. Dr Carol Cheung has given an overview of the use of these agents in haematological malignancies, and Dr Karen Tang has discussed in detail the applications of monoclonal antibodies in the treatment of multiple myeloma.

Allogeneic haematopoietic stem cell transplantation (HSCT) has been used for more than decades in the management of leukaemias. With its associated graft versus tumour effect, HSCT represents a form of adoptive cellular immunotherapy. Dr Joycelyn Sim and Dr Garret Leung have reviewed the recent advances in allogeneic HSCT focusing on haploidentical HSCT. A more target-specific adoptive cellular immunotherapy is chimeric antigen receptor (CAR)-T-cell therapy that involves genetic modification of T-lymphocytes to enhance their anti-cancer activities. In his article, Dr Thomas Chan has explained the concept of CAR-T cell therapy and discussed its use in lymphoid neoplasms.

In Haematology and Oncology, we often talk about precision medicine. For good watches, precision is also the key! In the Lifestyle of this Issue, Dr Herman Liu would share with the readers his extraordinary collection of wrist watches, showcasing a number of beautiful and highly sought-after timepieces.

Immune Checkpoint Blockade in the Management of Haematological Malignancies

Prof KWONG Yok-lam

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Prof KWONG Yok-lam

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2022.

INTRODUCTION

Immune checkpoints provide a regulatory mechanism to control the activation of effector cells in the immune response.[1] Generally, these immune checkpoints are represented by receptors on effector cells, which on ligation with their cognate ligands, transduce signals that inhibit cellular functions. Immune checkpoints play important roles in maintaining a balance in immune reactions. Malignant cells may hijack these regulatory pathways by over-expressing the cognate ligands of immune checkpoint receptors. Hence, although immune effector cells may recognise and target neoantigens on these malignant cells, ligation of the immune checkpoints with their cognate ligands expressed on malignant cells result in inhibition of the immune response. This immune escape leads to suppressed immunosurveillance, enhancing the proliferation of malignant cells.[2] Blockade of immune checkpoint receptors or their cognate ligands restores immunoreactivity of effector cells, thus constituting an innovative approach to cancer immunotherapy.

THE PD1-PDL1/L2 PATHWAY

The programmed cell death protein 1 (PD1) is an immune checkpoint receptor expressed on activated CD4+ and CD8+ T-cells, B-cells, natural killer (NK) cells, macrophages and dendritic cells.[3] It binds to two ligands, PDL1 and PDL2. On binding its ligand, PD1 inhibits immune cellular function. Blockade of the PD1/PDL1 pathway is currently the predominant immunotherapeutic strategy for haematological malignancies.[2]

MECHANISMS OF PD-L1/L2 OVER-EXPRESSION IN HAEMATOLOGICAL MALIGNANCIES

The prototypes of haematological malignancy over-expressing PDL1/L2 are classical Hodgkin lymphoma (cHL) and lymphomas infected with the Epstein Barr virus (EBV). In the neoplastic Hodgkin Reed-Sternberg cells of cHL, amplification of chromosome 9p24.1 (where the gene loci of PDL1/L2 are located) and JAK/STAT pathway activation are typically found.[4] Both mechanisms lead to PDL1 and PDL2 over-expression. In EBV-positive lymphomas, the viral oncoprotein LMP1 transactivates the *PD-L1* gene, resulting in PD-L1 over-expression.[5] Hence, targeting the PD1-PDL1/L2 pathway is an effective treatment for these malignancies.

PD1 BLOCKADE IN cHL

Two anti-PD1 antibodies nivolumab and pembrolizumab have been found to be highly effective for relapsed/refractory cHL, both now considered a standard-of-care for these patients.[6] An overall response rate (ORR) of 69%-75% and complete response rates (CR) of 16% - 23% were achieved in pivotal clinical trials in relapsed/refractory patients. More recently, pembrolizumab has shown promising results when combined with standard chemotherapy in newly-diagnosed cases of cHL.[7]

LOW-DOSE ANTI-PD1 BLOCKADE IN cHL

The standard doses of pembrolizumab and nivolumab for treating cHL are respectively 200 mg every three weeks (Q3W) and 240 mg Q2W or 480 mg Q4W. However, a direct dose-response relationship has not been established for anti-PD1 antibodies. High doses of anti-PD1 antibodies do not improve outcomes. However, adverse events are increased. Furthermore, health costs are substantially elevated.

At Queen Mary Hospital, we have adopted a low-dose anti-PD1 approach in treating cHL. Pembrolizumab is used at 100 mg Q3W, whereas nivolumab is used at 40 mg Q2W. In relapsed/refractory cHL, low-dose pembrolizumab and nivolumab achieved ORR of 100%, and CR of 67%-73%.[8-11] Results are at least comparable with, if not actually superior to, those in pivotal clinical trials. These results were achieved with very low rates of adverse events and significantly lower health costs. This low-dose approach has been validated independently by other researchers.[12]

PD1/PDL1 BLOCKADE IN NK (NATURAL KILLER)/T-CELL LYMPHOMA

NK/T-cell lymphomas are universally infected by EBV, representing the prototype of EBV-infected lymphoid malignancy.[13] In the first series of patients with

relapsed/refractory NK/T-cell lymphoma, treatment with pembrolizumab resulted in an ORR of 100% and a CR of 71%.[14] Treatment with nivolumab also resulted in high efficacies.[15] These results have been validated in a smaller number of patients treated with pembrolizumab.[16] In treating these patients, we have again adopted a low-dose approach with pembrolizumab and nivolumab, and shown that such a strategy is also effective in NK/T-cell lymphomas.[13,15]

Two other antibodies targeting the PD1/PDL1 pathway have also been evaluated in relapsed/refractory NK/T-cell lymphoma. The anti-PD1 antibody sintilimab induced an ORR of 68% in 28 patients.[17] The anti-PDL1 antibody avelumab induced an ORR of 38% with a CR of 24% in another study.[18]

These results have established the blockade of the PD1/PDL1 pathway as a standard salvage option for NK/T-cell lymphoma.[13] Preliminary results indicated structural changes in the 3'-UTR of the PDL1 gene to be associated with a more favourable response to pembrolizumab.[19] However, further studies are needed to define better clinicopathologic or genetic markers predictive of response to PD1/PDL1 blockade.

PD1 BLOCKADE IN OTHER LYMPHOMAS

Primary mediastinal large B-cell lymphoma (PMBCL) is a specific B-cell lymphoma localised to the mediastinum, with a predilection for young women. Relapsed/refractory PMBCLs respond very poorly to conventional therapy. In two clinical trials studying 74 patients with relapsed/refractory PMBCL, treatment with pembrolizumab led to an ORR of 46% and CR of 19%,[20] representing very good efficacy for these largely incurable patients.

Besides these results, blockade of the PD1/PDL1 pathway in other lymphomas has only shown anecdotal success. Reported lymphoid malignancies to respond to pembrolizumab included Richter transformation of chronic lymphocytic leukaemia (ORR: 44%),[21] relapsed/refractory mycosis fungoides/Sezary syndrome (ORR: 38%; CR: 8%)[22], double-hit lymphoma,[23] post-transplantation lymphoproliferative diseases,[24] and anaplastic large cell lymphoma[25] after allogeneic haematopoietic stem cell transplantation (HSCT).

Nivolumab has also been shown anecdotally to be effective in primary central nervous system diffuse large B-cell lymphoma,[26,27] testicular lymphoma,[26] and T-lymphoblastic lymphoma after allogeneic HSCT.[28]

ADVERSE EFFECTS OF PD1/PDL1 BLOCKADE

Blockade of the PD1/PDL1 pathway results in a distinctive array of adverse events, collectively known as immune related adverse events (irAE).[29,30] Virtually every organ in the body may be affected, but frequently affected sites include the skin, gut, liver, endocrine organs, lungs, kidneys, and the nervous system (Table 1).[2,29,30] Many of these irAEs resemble autoimmune conditions. Hence, patients with a history of autoimmune diseases are generally considered not suitable for PD1/PDL1 blockade. Furthermore, treatment with anti-PD1/PDL1 may exacerbate graft-versus-host disease after allogeneic HSCT.[31] Hence, a washout period is mandatory in patients treated with PD1/PDL1 blockade before undergoing allogeneic HSCT.

The severity of irAEs correlates with the dosage and duration of anti-PD1/PDL1 treatment. With our low-dose approach, irAEs are relatively mild and uncommon, with the lungs, thyroid and pituitary glands most often affected.[11] We recommend routine chest radiographs, thyroid function test and morning cortisol levels before each anti-PD1 treatment, in addition to vigilance against other known irAEs.

Table 1. Immune-related adverse events (Developed by author)

Site or organ	Manifestations
Skin	Rashes, dermatitis, Stevens-Johnson syndrome, vitiligo
Gastrointestinal tract	Oral mucositis, xerostomia, pancreatitis, colitis, enteritis, hepatitis
Endocrine system	Hypothyroidism, hypophysitis, diabetes mellitus, hypoadrenalism
Lungs	Pneumonitis
Nervous system	Encephalitis, meningitis, peripheral neuropathy
Musculoskeletal	Arthritis, myositis, vasculitis
Kidneys	nephritis
Bone marrow	Anaemia, thrombocytopenia
Cardiovascular system	Myocarditis, pericarditis, heart failure

THE CD47/SIRPα PATHWAY

The signal regulatory protein alpha (SIRPα) is an immune checkpoint receptor on macrophages, which on activation transduces an inhibitory signal that prevents phagocytosis.[32] Its cognate ligand is CD47, which is expressed on a variety of cells and constitutes a "don't eat me" signal preventing macrophage mediated phagocytosis. Malignant cells may express CD47, thereby avoiding their phagocytosis by macrophages.

Treatment with the anti-CD47 antibody magrolimab was first reported to be active when combined with rituximab in relapsed/refractory lymphomas, inducing an ORR of 40% (CR: 30%) in diffuse large B-cell lymphoma, and an ORR of 71% (CR: 43%) in follicular lymphoma.[33] Another CD47 targeting molecule TTI-621 (SIRPaFc serving as a decoy receptor) has also shown promising efficacies in phase 1 studies for a variety of hematologic malignancies[34] and mycosis fungoides/Sezary syndrome.[35]

Most of the development of anti-CD47 is now focused on myeloid malignancies, including acute myeloid leukaemia and myelodysplastic syndrome.[32,36] Clinical trials are conducted in combining anti-CD47 with hypomethylating agents, and have shown promising results.

TARGETING OTHER IMMUNE CHECKPOINTS IN HAEMATOLOGIC MALIGNANCIES

Other important immune checkpoints that have been considered therapeutic targets include lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin domain 3 (TIM3), and T cell immunoreceptor with Immunoglobulin and ITIM domains (TIGIT).[6] The targeting of these immune checkpoint proteins is tested in ongoing clinical trials in various haematological malignancies, including lymphomas and leukaemias.

IMMUNE CHECKPOINT TARGETING AND CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY

CAR-T cell therapy is a novel cellular therapy currently developed and approved for the treatment of B-cell malignancies. Over-expression of immune checkpoint receptors on CAR-T cells is one of the mechanisms for the failure of the therapy.[37] Accordingly, patients failing CAR-T cell therapy have been treated with anti-PD1 antibodies, leading to modest results.[38,39] Further work is therefore required to understand how immune checkpoint blockade may improve the therapeutic efficacy of CAR-T cells.

CONCLUSION

Immune checkpoint blockade is rapidly becoming a standard-of-care in haematological malignancies. However, many malignancies do not respond to such a strategy. Furthermore, for malignancies that respond, predictive markers have still not been defined. More studies are therefore needed in these areas, so that the efficacy of immune checkpoint blockade and the spectrum of responding haematological malignancies can be improved.

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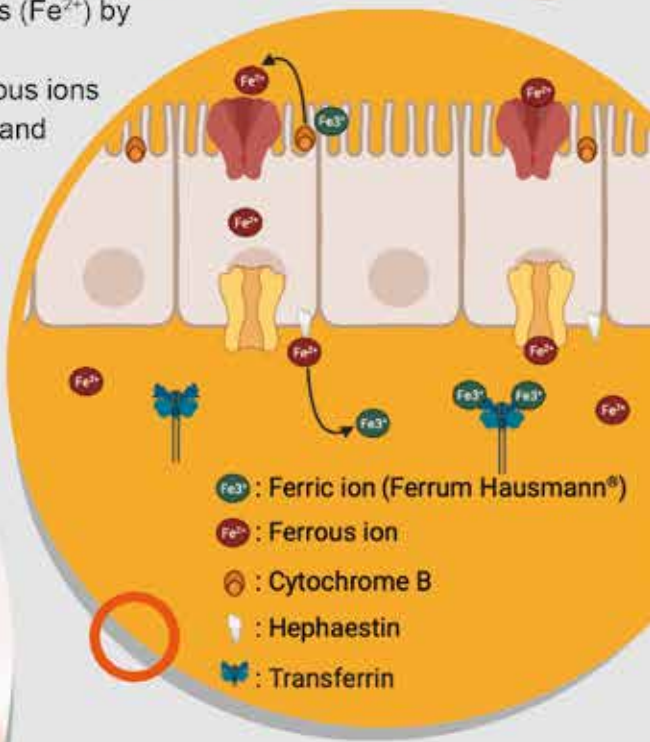

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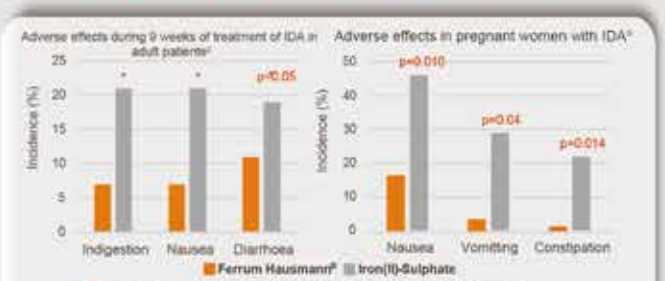

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CrCl, creatinine clearance; DDIs, drug-drug interactions; DHHS, Department of Health and Human Services; EACS, European AIDS Clinical Society; FTC, emtricitabine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IAS, International AIDS Society; INSTI, integrase strand transfer inhibitor; PLHIV, people living with HIV; STR, single-tablet regimen; TAF, tenofovir alafenamide.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Immune Checkpoint Blockade in the Management of Haematological Malignancies" by Prof KWONG Yok-lam and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Cancer cells may evade immune surveillance by over-expressing the cognate ligands of immune checkpoint receptors.**
2. **Immune checkpoint blockade therapy directly targets cancer cells leading to cancer cell apoptosis.**
3. **Programmed death protein ligand 1 (PD-L1) is the only ligand for PD1.**
4. **Anti-PD1/PD-L1 antibodies are the only available immune checkpoint blockade therapeutic agents available in the market.**
5. **Anti-PD1 antibodies are highly effective for relapsed/refractory classical Hodgkin's lymphoma with an overall responses rate of around 70-80 %.**
6. **Low-dose anti-PD1 antibodies are ineffective in the treatment of relapsed/refractory classical Hodgkin lymphoma.**
7. **PD-1 immune checkpoint blockade is largely ineffective in the treatment of primary mediastinal B-cell lymphoma.**
8. **There is no safety concern for the use of PD1/PD-L1 immune checkpoint blockade therapy in patients after allogeneic haematopoietic stem cell transplantation.**
9. **Cancer cells may express CD47, which binds signal regulatory protein alpha (SIRPα) on macrophages and inhibits phagocytosis by macrophages.**
10. **Chimeric antigen receptor T-cell (CAR-T) therapy is another form of immune checkpoint blockade therapy.**

ANSWER SHEET FOR DECEMBER 2022

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Immune Checkpoint Blockade in the Management of Haematological Malignancies

Prof KWONG Yok-lam

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Chair Professor of Haematology and Haematological Oncology
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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

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Answers to November 2022 Issue

Management of Psoriasis - Where Are We Now?

1. F 2. F 3. T 4. F 5. F 6. T 7. T 8. T 9. T 10. F

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(HR=0.56; 95% CI, 0.42–0.76; P=0.0002)[4]

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28.0 months (95% CI, 16.3–NE) **with MYLOTARG + chemo**

vs

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(HR=0.53; 95% CI, 0.36–0.76; P=0.0006)[4]

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*NCCN: recommended for newly diagnosed patients with AML, in combination with daunorubicin and cytarabine[1]. NICE: recommended with daunorubicin and cytarabine, as an option in untreated *de novo* CD33-positive AML, except acute promyelocytic leukaemia, in people aged 15 years and over[2].
†For patients aged 15 years and above only[3].

CI, confidence interval; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; NE, not estimable; NICE, National Institute for Health and Care Excellence.

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MYLOTARG® Summary of Product Information

TRADE NAME: MYLOTARG® (gemtuzumab ozogamicin). **PRESENTATION:** 5 mg powder for concentrate for solution for infusion. **INDICATIONS:** MYLOTARG is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, *de novo* CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL). **DOSAGE: Induction:** 3 mg/m^2/dose (up to a maximum of one 5 mg vial) infused over a 2-hour period on Days 1, 4, and 7 in combination with DNR 60 mg/m^2/day infused over 30 minutes on Day 1 to Day 3, and AraC 200 mg/m^2/day by continuous infusion on Day 1 to Day 7. If a second induction is required, MYLOTARG should not be administered during second induction therapy. Only DNR and AraC should be administered during the second induction cycle, at the following recommended dosing: DNR 35 mg/m^2/day on Days 1 and 2, and AraC 1 g/m^2 every 12 hours, on Day 1 to Day 3. **Consolidation:** For patients experiencing a complete remission (CR) following induction, up to 2 consolidation courses of intravenous DNR (60 mg/m^2 for 1 day [first course] or 2 days [second course]) in combination with intravenous AraC (1g/m^2 per 12 hours, infused over 2 hours on Day 1 to Day 4) with intravenous MYLOTARG (3 mg/m^2/dose infused over 2 hours up to a maximum dose of one 5 mg vial on Day 1) are recommended. Dose modification of MYLOTARG may be required based on individual safety and tolerability. Management of some adverse reactions may require dose interruptions or permanent discontinuation of MYLOTARG. Refer to the full prescribing information for complete recommendation. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS & PRECAUTIONS: Hepatotoxicity, including VOD/SOS:** Hepatotoxicity, including life-threatening, and sometimes fatal hepatic failure and VOD/SOS have been reported in patients treated with MYLOTARG. Based on an analysis of potential risk factors, adult patients who received MYLOTARG as monotherapy, either before or after an haematopoietic stem cell transplant (HSCT), and patients with moderate or severe hepatic impairment are at increased risk for developing VOD. Signs and symptoms of VOD/SOS should be closely monitored; these may include elevations in ALT, AST, total bilirubin, and alkaline phosphatase, which should be monitored prior to each dose of MYLOTARG, hepatomegaly (which may be painfull, rapid weight gain, and ascites. For patients who develop abnormal liver tests, more frequent monitoring of liver tests and clinical signs and symptoms of hepatotoxicity is recommended. For patients who proceed to HSCT, close monitoring of liver tests is recommended during the post-HSCT period, as appropriate. The ALFA-0701 study recommended an interval of 2 months between the last dose of MYLOTARG and HSCT although no definitive relationship was found between VOD and time of HSCT relative to higher MYLOTARG monotherapy doses. Management of signs or symptoms of hepatic toxicity may require a dose interruption, or discontinuation of MYLOTARG. In patients who experience VOD/SOS, MYLOTARG should be discontinued and patients treated according to standard medical practice. **Myelosuppression:** Complete blood counts should be monitored prior to each dose of MYLOTARG and signs and symptoms of infection, bleeding/haemorrhage, and other effects of myelosuppression should be monitored during treatment. Routine clinical and laboratory surveillance testing during and after treatment is indicated. Management of patients with severe infection, bleeding/haemorrhage, or other effects of myelosuppression, including severe neutropenia or persistent thrombocytopenia, may require a dose delay or permanent discontinuation of MYLOTARG. **Infusion-related reactions (including anaphylaxis):** Infusion of MYLOTARG should be performed under close clinical monitoring, including pulse, blood pressure, and temperature. Pre-medication with a corticosteroid, antihistamine and acetaminophen (or paracetamol) is recommended 1 hour prior to dosing. Interrupt the infusion for patients who develop evidence of severe reactions, especially dyspnoea, bronchospasm, or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of treatment should be strongly considered for patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension. **Tumor lysis syndrome (TLS):** Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice. Appropriate measures to help prevent the development of tumour lysis-related hyperuricaemia, such as hydration, administration of antihyperuricemics (e.g., allopurinol) or other agents for treatment of hyperuricaemia (e.g., rasburicase) must be taken. **AML with adverse-risk cytogenetics:** For patients being treated with MYLOTARG in combination with daunorubicin and cytarabine for newly diagnosed *de novo* AML, when cytogenetics testing results become available it should be considered whether the potential benefit of continuing treatment with MYLOTARG outweighs the risks for the individual patient. **INTERACTIONS:** No clinical drug interaction studies have been conducted with MYLOTARG. **PREGNANCY AND BREAST FEEDING:** Women of childbearing potential should avoid becoming pregnant while receiving MYLOTARG. Women of childbearing potential, or partners of females of childbearing potential should be advised to use 2 methods of effective contraception during treatment with MYLOTARG for at least 7 months (females) or 4 months (males) after the last dose. MYLOTARG must not be used during pregnancy unless the potential benefit to the mother outweighs the potential risks to the foetus. Pregnant women, or patients becoming pregnant while receiving MYLOTARG, or treated male patients as partners of pregnant women, must be apprised of the potential hazard to the foetus. Because of the potential for adverse reactions in breast-fed children, women must not breast-feed during treatment with MYLOTARG and for at least 1 month after the final dose. There is no information on fertility in patients. Both men and women must seek advice for fertility preservation before treatment. **SIDE EFFECTS:** VOD/SOS, haemorrhage, severe infection, tumour lysis syndrome, infusion related reactions, pyrexia, nausea, chills, vomiting, thrombocytopenia, fatigue, headache, stomatitis, abdominal pain, and neutropenia. Refer to the full prescribing information for complete recommendation.
Reference: MYLOTARG Hong Kong Prescribing Information (Version Jul 2021)
Date of Preparation: Feb2022
Identifier Number: MYL00222
Full Prescribing Information is available upon request.

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PP-MYL-HKG-0060 MAR2022

Bispecific Antibodies and Monoclonal Antibody Conjugates for Haematological Malignancies

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INTRODUCTION

Immunotherapy is gaining importance in the management of haematological malignancies. Indeed, monoclonal antibodies (MAb) have become the standard of care in certain blood cancers for years. Rituximab was the first ever immunotherapy approved for use in cancer and the year 2022 marks the 25th anniversary of its approval by the U. S. Food and Drug administration (FDA).[1,2] Nowadays, it is the backbone of treatment for various B-cell malignancies. Rituximab is considered a type of "naked" therapeutic monoclonal antibody which is typically bivalent and mono-specific IgG molecule. Modern technology enables the engineering and modification of MAb to enhance their efficacy. In particular, two approaches are commonly adopted, namely bispecific antibodies and monoclonal antibody conjugates.[3] Unlike the naked MAb, bispecific antibodies target two independent antigens or epitopes via various designs, often linking an effector cell, such as T-cell to a target cell.[4] Monoclonal antibody conjugates refer to MAb linked to a specific anti-tumour effector molecule, commonly a cytotoxic drug or radioactive particle. Antibody-drug conjugates (ADC) consist of MAb conjugated to a cytotoxic drug (also known as payload) via a chemical linker.[5] This review will focus on the clinical application of bispecific antibodies and antibody-drug conjugates in the management of haematological malignancies (Table 1).

Table 1. Immunotherapeutic agents covered in this article (Table prepared by author)

	Bispecific antibody	Antibody-drug conjugate
Acute lymphoblastic leukaemia	Blinatumomab	Inotuzumab ozogamicin
Acute myeloid leukaemia		Gemtuzumab ozogamicin
Non-Hodgkin B-cell lymphomas	Mosunetuzumab Glofitamab	Polatuzumab vedotin Moxetumomab pasudotox-tdfk
Hodgkin lymphoma and mature T-cell lymphoma		Brentuximab vedotin
Multiple myeloma		Belantamab mafodotin-blmf

ACUTE LYMPHOBLASTIC LEUKAEMIA

Acute lymphoblastic leukaemia (ALL) is a serious, deadly blood cancer. Despite its high initial complete remission (CR) rate with intensive conventional combination chemotherapy, a significant proportion of patients eventually relapse and the long-term survival of adult ALL patients is around 40% only.[6] In recent years, immunotherapy has been formally incorporated into the management of ALL following the approval of two new immunotherapeutic agents, namely blinatumomab and inotuzumab ozogamicin. Both drugs were shown to be superior to conventional chemotherapy in relapsed or refractory ALL, leading to significant improvement in clinical outcomes.

Blinatumomab

Blinatumomab is a type of bispecific antibodies termed bispecific T-cell engager (BiTE®). It has dual specificity for CD3 and CD19. Most B-lineage ALL (B-ALL) blasts express CD19, while CD3 is expressed on the surface of T-cells. By simultaneous binding to CD3-positive cytotoxic T-cells and CD19-positive blasts, blinatumomab activates the patient's endogenous T-cells to recognise and eliminate the leukaemic cells. Currently, blinatumomab is approved for the treatment of relapsed or refractory CD19-positive B-ALL in adult and paediatric patients, as well as those in first or second remission with minimal residual disease (MRD) greater than or equal to 0.1%. Its efficacy over conventional chemotherapy was established in the landmark TOWER trial.[7] In patients with relapsed/refractory Philadelphia chromosome (Ph)-negative B-ALL, complete remission (CR) rate was significantly higher in the blinatumomab group than the chemotherapy group (44% vs 25%). The blinatumomab group also had a significantly longer median duration of remission and overall survival.

Minimal or measurable, residual disease (MRD) refers to the low-level disease that is below the detection limit of conventional cytomorphology. The role of MRD is increasingly appreciated in the field of malignant haematology and it is considered an important independent prognostic factor in ALL.[8] Blinatumomab has been proven in the BLAST trial[9] to be an effective treatment for the clearance of MRD that persists after standard chemotherapy. In this single-arm study, blinatumomab was given to B-ALL patients who were in haematologic CR with persistent or recurrent MRD greater than or equal to 0.1% after at least three blocks of intensive chemotherapy. Seventy-eight percent of patients achieved a complete MRD response, which was associated with longer relapse-free survival (RFS) and overall survival (OS).

Due to its short half-life, blinatumomab is administered as continuous intravenous infusion for 28 days per

cycle. Its major side effects include cytokine release syndrome (CRS) and neurological toxicity, with the risks being much lower when given in the MRD setting than relapsed/refractory disease. Outside its licensed indications, the therapeutic role of blinatumomab in the front-line setting has also been actively investigated in recent years, and the clinical data are promising.[10-12]

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is an ADC directed against CD22, which is expressed in more than 90% of B-ALL patients. It consists of a humanised monoclonal antibody and a cytotoxic agent called calicheamicin, covalently attached together via an acid labile linker. The ADC binds to CD22-expressing ALL blasts, followed by internalisation of the CD22-conjugate and intracellular release of calicheamicin. Calicheamicin induces double-strand DNA breaks, and hence apoptotic cell death. Inotuzumab is approved for the treatment of relapsed or refractory B-ALL in adults. In the phase 3, randomised INO-VATE trial[13], the CR rate was significantly higher in the inotuzumab group than in the conventional chemotherapy group (80.7% vs 29.4%). Progression-free survival (PFS) was also significantly longer in the inotuzumab group.

Inotuzumab is administered intravenously and offers a more convenient treatment schedule than blinatumomab. It is given on day 1, day 8 and day 15 of a 3- to 4-week cycle, dosage and cycle length depending on the response to the treatment. Apart from infusion-related reactions commonly associated with MAb, inotuzumab carries a black-box warning concerning the risk of hepatotoxicity including hepatic veno-occlusive disease (VOD). Almost a quarter of patients who underwent allogeneic haemopoietic stem cell transplantation (HSCT) after inotuzumab treatment experienced VOD.[14] It is postulated that VOD develops as a result of the injury caused to sinusoidal endothelial cells by the calicheamicin component of the ADC.[15] The same toxicity is also observed in gemtuzumab ozogamicin, another ADC containing calicheamicin and used in patients with acute myeloid leukaemia (AML). Due to the risk of VOD, it is recommended that patients proceeding to HSCT should receive no more than two cycles of inotuzumab.

Although the approval of inotuzumab is based on its administration as monotherapy, its safety and efficacy when given as a combination treatment with conventional chemotherapeutic agents as well as blinatumomab have been explored.[16,17] It is foreseeable that these monoclonal antibodies, together with CAR T-cell therapy, will continue to reshape the treatment landscape of ALL.

ACUTE MYELOID LEUKAEMIA

Acute myeloid leukaemia (AML) is a more common form of acute leukaemia in adults than ALL.[18] For decades, the standard induction therapy for AML had been the "7+3 regimen", comprising 7 days of cytarabine and 3 days of anthracycline. However, a number of new drugs have been approved for the treatment of AML by the FDA since 2017, one of which being gemtuzumab ozogamicin.[19]

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is an ADC directed against CD33, which is commonly expressed on myeloid blasts. Similar to inotuzumab, it consists of a MAb covalently linked to the cytotoxic agent calicheamicin. The anti-leukaemic activity of the drug is exerted by the intracellular release of calicheamicin in the CD33-expressing tumour cells, following the binding of the ADC to the tumour cells and internalisation of the ADC-CD33 complex. In fact, GO was first granted accelerated approval by the FDA in 2000 for the treatment of older adults with relapsed CD33-positive AML. At that time, the recommended regimen was 9 mg/m^2 for two doses 14 days apart. However, its manufacturer voluntarily withdrew the drug from the market in 2010 as a result of safety concerns and lack of clinical benefit in a phase 3 trial which evaluated GO 6 mg/m^2 in combination with 7+3 induction in newly diagnosed AML patients.[20] Further studies adopted a fractionated dosing schedule to reduce the toxicities. In 2017, GO gained approval again at a lower recommended dose and a different treatment schedule for the treatment of newly diagnosed and relapsed or refractory CD33-positive AML. In the randomised, phase 3 ALFA-0701 trial[21], a fractionated dose of GO in combination with standard front-line chemotherapy was shown to significantly improve the event-free survival in adult AML patients (median 17.3 months vs 9.5 months).

GO is given as an intravenous infusion. Its dosage and dosing schedule vary according to the indication. For patients with newly diagnosed AML, the recommended dose of GO is 3 mg/m^2 on Days 1, 4, and 7 in combination with daunorubicin and cytarabine during the induction cycle. GO should be given on Day 1 only in the consolidation cycles. In relapsed/refractory cases, GO is given as a single agent. Apart from hepatotoxicity including VOD, GO is also associated with a higher rate of haemorrhage and a longer median time to platelet recovery. Given the toxicity profile of GO, extra precautions should be taken to mitigate the risks of VOD and thrombocytopenia.[22]

LYMPHOMA

Immunotherapy plays an important role in the management of lymphoma. A number of MAb have been approved for the treatment of various subtypes of lymphoma. While CD20 remains a common target, some MAb are directed to other surface antigens that are frequently expressed on mature B-cell lymphomas, such as CD22 and CD79b. On the other hand, CD30 is expressed in classical Hodgkin lymphoma and certain types of T-cell lymphoma; thus has become the target of immunotherapy.

Non-Hodgkin B-cell Lymphomas

Mosunetuzumab is a novel CD20xCD3 T-cell engaging bispecific antibody. It was granted conditional marketing authorisation by the European Commission (EC) in June 2022 for the treatment of relapsed or refractory follicular lymphoma (FL). It was also granted Priority Review by the FDA, which was expected to decide on the approval by the end of 2022. In the

pivotal phase I/II study, mosunetuzumab was shown to have high complete response (CR) rates and durable remission in heavily pre-treated patients with relapsed or refractory FL.[23] Unlike blinatumomab, which is a fragment-based bispecific antibody and does not contain an Fc region, mosunetuzumab is a full-length, humanised bispecific antibody. It recruits endogenous T cells to engage and kill CD20-expressing B cells. Its structure confers more favourable pharmacokinetic properties, and the drug can be given intravenously once every 21-day cycle, after the initial step-up phase. Cytokine release syndrome (CRS) is a notorious side effect of T-cell activating therapies such as bispecific T-cell engaging antibodies and adoptive T-cell therapies, and mosunetuzumab is no exception.

Glofitamab is another CD20xCD3 T-cell engaging bispecific antibody of interest. It differs from mosunetuzumab in the number of antigen-binding fragment (Fab) arms: glofitamab has a 1:2 CD3:CD20 ratio, while mosunetuzumab has a 1:1 CD3:CD20 ratio. It is postulated that such CD20 bivalency might be associated with better potency against tumour. Glofitamab has not been approved yet, but the preliminary clinical data are encouraging.[24]

ADCs approved for the treatment of B-cell lymphoma include polatuzumab vedotin and moxetumomab pasudotox-tdfk. Polatuzumab vedotin is a CD79b-directed ADC. In combination with bendamustine and rituximab, it is indicated for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In the randomised trial[25] that compared polatuzumab in combination with bendamustine and rituximab (pola-BR) versus BR in transplantation-ineligible relapsed/refractory DLBCL, the former had a significantly higher CR rate (40.0% vs 17.5%), and longer PFS and OS. Pola-BR was associated with high rates of myelosuppression and peripheral neuropathy. Progressive multifocal leukoencephalopathy (PML) has also been rarely reported after treatment with polatuzumab. The role of polatuzumab in front-line setting has been investigated in the POLARIX trial, which compared pola-R-CHP (polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone) against the current standard-of-care R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).[26] While the pola-R-CHP group had a higher EFS, there was no significant difference in the overall response rate and OS.

Moxetumomab pasudotox-tdfk is a CD22-directed immunotoxin and is indicated for the treatment of relapsed or refractory hairy cell leukaemia (HCL) in adult patients. Unlike a typical ADC which comprises a chemical linker connecting the MAb and cytotoxic payload, moxetumomab consists of an anti-CD22 antibody conjugated to a toxin by recombinant DNA technology.[27] The efficacy of moxetumomab in relapsed/refractory HCL was demonstrated in a multi-centre, single-arm, open-label study which led to its FDA approval.[28] It is associated with unique toxicities including capillary leak syndrome and haemolytic uraemic syndrome, the mechanism of which remains poorly understood.

OTHER LYMPHOMAS

Brentuximab Vedotin

Brentuximab vedotin (BV) is a CD30-directed ADC. CD30 expression is commonly found in classical Hodgkin's lymphoma (cHL) and certain types of mature T-cell lymphoma, e.g. anaplastic large cell lymphoma (ALCL). BV is indicated for the treatment of cHL, systemic ALCL, and other CD30-expressing peripheral T-cell lymphomas (PTCL) as well as mycosis fungoides (MF). In the multi-centre, randomised phase 3 ECHELON-1 trial[29], BV in combination with doxorubicin, vinblastine and dacarbazine (A+AVD) was shown to result in a higher modified PFS than ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) (82.1% vs 77.2%). In the latest updated analysis of ECHELON-1 with 6-year follow-up[30], the A+AVD group also significantly reduced the risk of mortality. On the other hand, the efficacy of BV in previously untreated mature T-cell neoplasms including anaplastic large cell lymphoma (ALCL) and other CD30-positive peripheral T-cell lymphomas, was evaluated in the ECHELON-2 trial.[31] The group using BV plus chemotherapy (cyclophosphamide, doxorubicin and prednisone) had superior PFS than the CHOP group (48.2 months vs 20.8 months). BV carries a similar toxicity profile to polatuzumab vendotin, such as peripheral neuropathy and PML.

MULTIPLE MYELOMA

Belantamab Mafodotin-blmf

The application of immunotherapy is expanding in multiple myeloma, too. Following approval of several monoclonal antibodies for the treatment of myeloma, namely daratumumab, elotuzumab, and isatuximab, belantamab mafodotin-blmf (belamaf) was the first ADC introduced to patients with relapsed or refractory multiple myeloma. Belamaf is a B-cell maturation antigen (BCMA)-directed ADC using the microtubular inhibitor monomethyl auristatin F (MMAF) as the payload. In the phase 2 DREAMM-2 study, around one-third of heavily pre-treated myeloma patients responded to single-agent belamaf.[32] Belamaf carries unique ocular toxicity. At its approved dose (2.5 mg/kg as an intravenous infusion once every 3 weeks), a majority of patients developed keratopathy of any grade associated with a change in visual acuity.[33] These changes in the corneal epithelium were thought to be related to MMAF. Ophthalmic examination should be conducted regularly, and prompt intervention should be offered once corneal events are observed.[34]

Lastly, BCMA is a major target for immunotherapy in multiple myeloma. A number of BCMA-directed bispecific antibodies are in development[35], not to mention ciltacabtagene autoleucel, the BCMA-directed CAR T-cell therapy approved for the treatment of relapsed or refractory multiple myeloma. It is anticipated these novel immunotherapeutic agents will be incorporated into the standard treatment regimens for myeloma.

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CONCLUSION

The past decade has been an exciting time for the field of haematological oncology. Immunotherapy, a new class of drugs, has been introduced to the management of various haematological malignancies and has led to a shift in the treatment paradigm. Some are approved as single-agent therapy (e.g. blinatumomab, belamaf), while others are used in conjunction with conventional chemotherapy (e.g. GO, polatuzumab). With mechanisms of action and pharmacologic properties different from conventional cytotoxic chemotherapy, these bispecific antibodies and ADC do have their unique safety profiles. For example, cytokine release syndrome and neurotoxicity are major side effects observed in bispecific T-cell engaging antibodies such as blinatumomab and mosunetuzumab. The cytotoxic payloads in ADC are often associated with important adverse events, such as VOD in calicheamicin-containing ADCs and keratopathy in MMAF-based ADCs. As the data mature and experience accumulates, it is likely that these immunotherapeutic agents will be moved to earlier lines of treatment to enhance efficacy and to improve long-term clinical outcomes in the years to come.

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Certificate Course for Doctors, Nurses and Health Care Providers • Course No. C389 • CME/CNE Course

Certificate Course on

Common Diseases in Otorhinolaryngology, Head & Neck Surgery 2023 *(Video Lectures)*

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society of Otorhinolaryngology, Head & Neck Surgery

Objectives:

Otorhinolaryngology is a specialty managing diseases over head and neck region and sleep related disorders. This course provides essentials about ENT conditions to health care providers. Participants will have latest information in the related topics to facilitate their daily practice in managing related ENT conditions and collaboration with ENT specialists.

Date	Topics	Speakers
5 January 2023	ENT Kids: How to Handle Them in Office, and When to Refer?	Dr Alice KY Siu Specialist in Otorhinolaryngology Hong Kong Children Hospital Clinical Assistant Professor (Honorary) Department of Otorhinolaryngology, Head and Neck Surgery The Chinese University of Hong Kong
12 January 2023	Update on Management of Head and Neck Cancer	Dr. Eddy Wong Chief of Service Department of Ear, Nose & Throat Prince of Wales Hospital
19 January 2023	Rhinosinusitis and its Management	Dr. Fergus Wong Associate Consultant Department of Ear, Nose & Throat Pamela Youde Nethersole Eastern Hospital
26 January 2023	Hearing Loss and its Related Treatment	Dr. Wai-tsz Chang Assistant Professor Department of Otorhinolaryngology, Head and Neck Surgery The Chinese University of Hong Kong
2 February 2023	Management of Challenging Voice Disorders	Dr. Eric Tang Specialist in Otorhinolaryngology Clinical Assistant Professor (Honorary) Department of Otorhinolaryngology, Head and Neck Surgery The Chinese University of Hong Kong
9 February 2023	Obstructive Sleep Apnea Syndrome – from Diagnosis to Management	Dr. Fiona Chui-yan Wong Specialist in Otorhinolaryngology Clinical Assistant Professor (Honorary) Department of Otorhinolaryngology, Head and Neck Surgery The Chinese University of Hong Kong

Dates : 5, 12, 19, 26 January & 2, 9 February 2023 (Thursday)
Time : 7:00 pm – 8:30 pm
Duration of session : 1.5 hours (6 sessions)
Course Feature : Video lectures (with Q&A platform for participants to post the questions)
Language Media : Cantonese (Supplemented with English)
Quiz for doctors : DOCTORS are required to complete a quiz after the completion of each lecture
Course Fee : HK$1,000
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline : 28 December 2022
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel: 2527 8898 Fax: 2865 0345 Email : vienna.lam@fmshk.org

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Monoclonal Antibodies in the Management of Myeloma

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INTRODUCTION

Significant advancements in the treatment of multiple myeloma (MM) have occurred over the last few years, improving the median survival of patients from 3-4 years to nearly one decade[1]. The key to such great success lies in the introduction of novel therapeutic agents. These drugs include: 1) the immunomodulatory agents (IMIDs) lenalidomide and pomalidomide; 2) the proteasome inhibitors (PIs) bortezomib, carfilzomib, and ixazomib; 3) monoclonal antibodies (MoAbs) daratumumab, elotuzumab, and isatuximab, and 4) antibody drug conjugate (ADC) belantamab mafodotin. These drugs can be used in combinations as triplets or quadruplets, leading to overwhelming response rates of up to 90% in newly diagnosed myeloma patients[2,3]. In particular, the response rates, progression-free survival (PFS) and overall survival (OS) reached by the use of anti-CD38 MoAbs daratumumab and isatuximab have been unprecedented in MM[4]. This article will focus on the MoAbs that are currently available and more widely used in Hong Kong, including daratumumab, isatuximab and belantamab. Developments in bispecific antibodies which may soon be available, will also be briefly summarised.

DARATUMUMAB

Daratumumab is a first-in-class human immunoglobulin G1 kappa (IgG1κ) CD38-directed MoAb. CD38 is an excellent therapeutic target in myeloma because it is expressed with relatively high surface density on abnormal plasma cells, whereas its expression is lower on normal myeloid and lymphoid cells[5,6]. Daratumumab can be given by intravenous infusion over 4-8 hours or subcutaneously within 5 minutes. Subcutaneous administration has a lower rate of infusion-related reactions (IRRs) and can significantly reduce drug administration time[7]. The subcutaneous formulation is not yet registered in Hong Kong but will likely be available in 2023. Daratumumab can be used in both transplant-eligible and transplant-ineligible newly diagnosed MM (NDMM) or relapse refractory MM (RRMM). Table 1 summarises the results of key pivotal trials on daratumumab.

Daratumumab in NDMM

Combination of daratumumab, bortezomib, thalidomide and dexamethasone (D-VTd) showed superior response rates, complete response (CR) rates, PFS, and a trend to better OS as compared with VTd, followed by autologous stem cell transplant (ASCT) in the phase III CASSIOPEIA trial[8]. The addition of daratumumab to bortezomib, lenalidomide and dexamethasone (D-VRd) followed by ASCT further increased the rate and depth of response to therapy, with a trend towards improved PFS in the phase II GRIFFIN trial[9]. In these trials, the benefit of daratumumab was observed in patients with both standard and high-risk disease, but was more pronounced in the former group of patients. With the current follow-up data, OS benefit has not been demonstrated with the addition of daratumumab to either triplet regimens. In these two trials, approximately one out of three patients in the daratumumab group achieved CR and sustained minimal residual disease (MRD)-negative status at 1 or 2 years, as compared with around only one-tenth of patients in the placebo group achieving the same depth of response.

For transplant-ineligible patients, significant superiority in response rates, CR rate, MRD negativity, PFS and OS with the addition of daratumumab was demonstrated in 2 phase III randomised studies comparing daratumumab, lenalidomide and dexamethasone (DRd) with Rd till disease progression (MAIA trial)[10], and daratumumab, bortezomib, melphalan and dexamethasone (D-VMP) with VMP (ALCYONE trial)[11]. Although the comparison between different trials should be made with caution, the median PFS of the patients treated with Rd in the MAIA trial was similar to those treated with Dara-VMP in the ALCYONE trial (33.8 vs 36 months), suggesting better performance of Dara-Rd compared with Dara-VMP in those ineligible for transplant[12]. However, there was a higher incidence of grade 3-4 infective complications in those receiving daratumumab, specifically pneumonia and upper respiratory infection, which should be taken into consideration in the management of elderly and frail myeloma patients.

Daratumumab in RRMM

At first relapse, for patients who are not refractory to lenalidomide, multiple triplet regimens can be considered, including DRd[13], carfilzomib lenalidomide dexamethasone (KRd)[14] and ixazomib lenalidomide dexamethasone (IRd)[15]. Each of these regimens has shown superiority over Rd in randomised trials. In the phase III POLLUX trial, DRd significantly improved response rates, PFS, and MRD-negativity rates as compared with Rd in patients regardless of cytogenetic risk[13]. The greatest clinical benefit of DRd was also observed in patients that had received one prior line

Table 1: Summary of trials for Daratumumab and Isatuximab (Developed by author)

Study Name	Combination Therapy	Median follow up, months	CR or better	Median PFS, months	Median OS, months	MRD negativity, 10-5
Daratumumab Trials						
CASSIOPEIA[8]	Dara VTd vs VTd (first randomisation) -> ASCT -> Dara MTN vs no MTN (second randomisation)	35.4 (from second randomisation)	73% vs 61%, p < 0.0001	NR vs 46.7, p < 0.0001	NR vs NR	59% vs 47%, p = 0.0001
GRIFFIN[9]	Dara VRd vs VRd -> ASCT -> Dara R MTN vs R MTN	38.6	82% vs 61%, p = 0.0013	NR vs NR (36 months PFS rate 88.9% vs 81.2%)	NR vs NR (36 months OS rate 92.6% vs 92.2%)	62.5% vs 27.2%, p < 0.0001
MAIA[10]	Dara Rd vs Rd	56.2	51% vs 30%, p < 0.0001	NR vs 34.3, p < 0.0001	NR vs NR, p = 0.0013 (60 months OS rate 66.3% vs 53.1%)	31% vs 10%, p < 0.0001
ALCYONE[11]	Dara VMP -> Dara MTN vs VMP x9 cycles	40.1	46% vs. 25%; p < 0.0001	36.4 vs 19.3, p < 0.0001	75 vs 62, p = 0.0003	28% vs. 7%, p < 0.0001
POLLUX[13]	Dara Rd vs Rd	44.3	56.6% vs 23.2%; p < 0.0001	44.5 vs 17.5, p < 0.0001	NR vs NR (42 months OS rate 65% vs 57%)	30.4% vs 5.3%; p < 0.0001
CANDOR[17]	Dara Kd vs Kd	27	33% vs 13%	28.6 vs 15.2, p < 0.0001	Pending maturity	18% vs 4%, p < 0.0001
APOLLO[18]	SC Dara Pd vs Pd	16.9	25% vs 4%, p < 0.0001	12.4 vs 6.9, p = 0.0018	Pending maturity	9% vs 2%
Isatuximab Trials						
ICARIA[26]	Isa Pd vs Pd	35.3	9.7% vs 2.7%	11.1 vs 5.9, p < 0.0001	24.6 vs 17.7, p = 0.028	NA
IKEMA[27]	Isa Kd vs Kd	44	44.1% vs 28.5%, OR 2.09, 95% CI 1.26 - 3.48	35.7 vs 19.2, HR 0.58, 95% CI 0.42 - 0.79	Pending maturity	33.5% vs 15.4%, OR 2.78, 95% CI 1.55 - 4.99
GMMG HD7[28]	Isa VRd vs VRd -> ASCT -> Isa R vs R MTN	NA	21.6% vs 24.2%, p = 0.46	Pending maturity	Pending maturity	50.1% vs 35.6%, p < 0.001

Abbreviations: Dara VTd, daratumumab bortezomib thalidomide dexamethasone; ASCT, autologous stem cell transplant; MTN, maintenance; Dara VRd, daratumumab bortezomib lenalidomide dexamethasone; Dara Rd, daratumumab lenalidomide dexamethasone; Dara VMP, daratumumab bortezomib melphalan prednisolone; Dara Kd, daratumumab carfilzomib dexamethasone; Dara Pd, daratumumab pomalidomide dexamethasone; Isa Pd, isatuximab pomalidomide dexamethasone; Isa Kd, isatuximab carfilzomib dexamethasone; Isa VRd, isatuximab bortezomib lenalidomide dexamethasone; NA, not available; CR, complete response; PFS, progression free survival; OS, overall survival; NR, not reached; MRD, minimal residual disease

Table 2. Safety and Efficacy of bispecifics (adapted from Moreau et al Blood 2022)(Excerpted from Reference 41)

	Teclistamab(36) N=159	Elranatamab(38) N=50	Talquetamab(39) N=95	Cevostamab(40) N=160
Target	BCMA	BCMA	GPRC5D	FcRH5
Phase	1/2	1	1	1
Administration	SC weekly	SC Q2 weeks	SC weekly or Q2 weeks	IV Q3 weeks
Median Prior lines	5 (2-15)	6	Not reported	6
Age	64	64	61	64
Triple refractory	77	98	81	85
RP2D	1.5 mg/kg/week	1 mg/kg	405 μg/kg weekly or 800 μg/kg Q2 weeks	Not reported
CRS, grade >= 3 (%)	67, 1	83, 0	73, 3 at 405 μg/kg weekly or 78, 0 at 800 μg/kg Q 2 weeks	80, 1
Neurotoxicity, grade >= 3 (%)	2.5, 0	Not reported	Not reported	13.1, 3.8
ORR (%)	65	70	70 at 405 μg/kg weekly or 71 at 800 μg/kg Q 2 weeks	36.7 at 90 mg 54.5 at 160 mg
DOR (%)	6 months, 90%	92.3% at 6 months	6 months: 67% at 405 μg/kg weekly	Median 15.6 months

Abbreviations: BCMA, B cell maturation antigen; GPRC5D, G protein-coupled receptor, class C group 5 member D; FcRH5, Fc receptor-homolog 5; SC, subcutaneous; IV, intravenous; CRS, cytokine release syndrome; ORR, overall response rate; DOR, duration of response

of therapy supporting the use of DRd in patients with RRMM at first relapse. Although these triplet combinations (DRd, KRd, IRd) have not been directly compared in prospective clinical trial, it is worth noting that DRd has produced the largest reduction in the risk of progression and was apparently better tolerated[16].

The effectiveness of other daratumumab triplet combinations has also been evaluated. In the phase III CANDOR trial, patients receiving daratumumab, carfilzomib and dexamethasone (DKd) had superior response rates, MRD negativity and PFS, as compared with those treated with Kd, and the benefits were demonstrated in all cytogenetic risk groups and patients with lenalidomide refractoriness[17]. Subcutaneous daratumumab, pomalidomide and dexamethasone (DPd) resulted in improved response rates, MRD negativity and PFS as compared with Pd in the phase III APOLLO trial[18]. Comparing the median PFS of patients receiving DKd (28.6 months) and DPd (12.4 months) may give the impression that DKd was superior to DPd. However, the different patient populations recruited in these two studies should be noted; lenalidomide-refractory patients in APOLLO constituted around 80% of the study population, as compared with 30% in the CANDOR trial. Patients with lenalidomide-refractory myeloma have unfavourable prognosis[19,20]. Quadruplet regimens in single arm studies combining daratumumab, carfilzomib, pomalidomide and dexamethasone (DKPd) have also shown good response rates and PFS in this poor risk group of patients[21,22].

How Do We Use Daratumumab?

The cost and the lack of government funding for daratumumab have limited the use of this effective agent in the management of myeloma patients in Hong Kong. In the public sector, daratumumab could be considered a patient self-financed item to combine with either VTd or VRd induction to improve the survival outcome of patients. A clinical trial examining the daratumumab, carfilzomib, lenalidomide and dexamethasone combination (DKRd) with an MRD-response-adapted approach (MASTER trial) has shown that patients with two or more high-risk cytogenetic aberrations lose MRD negative response more readily during the treatment-free period, leading to shorter PFS and OS[23]. Based on these data and our present limited understanding of disease relapse dynamics, I would suggest high-risk patients (i.e. those with high-risk cytogenetics) continue daratumumab in addition to either lenalidomide or bortezomib maintenance after induction with careful balance and monitoring of their underlying infective risks. For patients not exposed to daratumumab initially, daratumumab-containing regimens should be used in the relapsed/refractory setting.

ISATUXIMAB

Isatuximab is a chimeric humanised IgG1 monoclonal antibody that binds to a specific epitope on the human cell surface antigen CD38. Isatuximab differs from daratumumab in its mechanism of action with higher antibody-dependent cytotoxicity[24], and it inhibits the CD38 enzymatic activity via allosteric inhibition[25]. Isatuximab is approved for the treatment of RRMM and is given by intravenous infusion. Table 1 summarises the results of clinical studies on isatuximab.

Isatuximab for RRMM

The phase III ICARIA MM study compared isatuximab, pomalidomide and dexamethasone (IsaPd) with PD in RRMM. The overall response rate was much higher in the IsaPd group, with a median PFS of 11.6 months as compared with 6.5 months in the Pd arm[26]. Another phase III trial IKEMA evaluated the use of isatuximab, carfilzomib and dexamethasone (IsaKd) versus Kd. IsaKd yielded significantly higher rates of CR and MRD negativity. The median PFS was significantly longer in the IsaPd group, 35.7 months, as compared with 19.2 months in the Kd group[27]. Though PFS associated with IsaKd may appear longer than IsaPd, these two studies again recruited different study populations, with over 90% of patients having lenalidomide-refractory disease in the ICARIA study. Isatuximab is currently not approved for use in NDMM, however promising results have been shown in the GMMG-HD7 phase III trial, with superior MRD negativity rates in the IsaRVd arm as compared with RVd after induction alone in NDMM[28].

How Do We Use Isatuximab?

With the increasing use of daratumumab in frontline treatment and RRMM, resistance to daratumumab is becoming a concern, and optimal management is largely unclear. Evidence suggests that daratumumab failure is mediated by clone selection of MM cells with lower CD38 expression as well as CD38 depletion in existing MM cells[29]. Sequential isatuximab treatment after daratumumab-refractory MM may be of limited benefit. If isatuximab treatment is to be considered after progression on daratumumab, patients with a longer gap of at least six months between daratumumab and isatuximab treatment may respond better[30,31]. Furthermore, it has been suggested that immune reconstitution following ASCT or CART cell therapy may rekindle sensitivity towards isatuximab, yielding better response rates[31]. At this point, I would use isatuximab in RRMM patients who are daratumumab-naïve or who have not been on daratumumab maintenance. The role of isatuximab in the treatment of patients with gain/amplification of chromosome 1q[32] and soft tissue plasmacytoma[33] in subgroup analyses of ICARIA and IKEMA have recently been brought to attention.

BELANTAMAB

Belantamab mafodotin is a first-in-class ADC consisting of an anti-B cell maturation antigen (BCMA) MoAb bound to the microtubule-disrupting agent, monomethyl auristatin F (MMAF). It is approved for patients with RRMM who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. Single agent belantamab gave an overall response rate of 32% and PFS of 11 months in a heavily pre-treated population with a median of seven prior lines of treatment[34]. Belantamab

can cause changes in the corneal epithelium resulting in alterations in vision, including severe vision loss, corneal ulcers and symptoms such as blurred vision and dry eyes. Ophthalmic examination should be conducted at baseline, before each dose, and promptly for worsening symptoms. Further trials looking into the combination of belantamab with other classes of anti-myeloma drugs are currently in progress, with the aim to maximise efficacy while allowing a more manageable toxicity profile[35].

BISPECIFIC T CELL ENGAGERS

Bispecific T-cell engagers are antibody-like molecules with two binding specificities: CD3 on T cells, and a tumour-associated antigen (this varies among the agents) on the cancer cells. Their use does not require apheresis and T-cell manipulation as in chimeric antigen receptor T-cell (CAR-T) therapy. Teclistamab, which targets BCMA, is the most advanced in development. In the MajesTEC-1 trial[36], 63.0% of the triple class–exposed patients achieved a response with 39.4% CR. Among patients with CR, 46.2% achieved MRD negativity. The overall duration of response was 18.4 months, and the median PFS was 11.4 months. The development of bispecific antibodies is ongoing, with several other products under investigation. They include other BCMA/CD3, CD38/CD3, FcRL5/CD3 and GPRC5D/CD3 bispecific antibodies (Table 2). If approved, additional off-the-shelf products with novel mechanisms of action will be available for patients with RRMM.

Positioning Different BCMA Targets

As of now, belantamab mafodotin is the only agent targeting BCMA available in Hong Kong and is the drug of choice for patients with progressive myeloma that are triple-class refractory. In the near future, when BCMA CAR-T cell therapy and bispecific T-cell engagers are made licensed in Hong Kong, fit patients may be considered for CAR-T therapy first and bispecific antibodies or ADC upon relapse after CAR-T. There are emerging data on retained efficacy of BCMA bispecific antibodies after failing BCMA ADC and BCMA CAR-T cell therapy[37,38]. On the other hand, bispecific antibodies or ADC may be the initial treatment of choice for frail patients with RRMM.

CONCLUSION

Antibody therapy has become an essential component of MM treatment in the past few years. Monoclonal antibodies were initially introduced for RRMM but now have an increasing role in the frontline setting. ADC and bispecific T-cell engagers are beginning to enter the treatment landscape and are needed to overcome resistance after multiple prior lines of therapy. Antibody therapy options for the treatment of MM continue to evolve and are achieving responses that are both deeper and more durable. Future directions should focus on better patient selection and sequencing of treatment regimens to further improve the outcome of patients with myeloma.

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Radiology Quiz

Dr John Yuen-hei MAK
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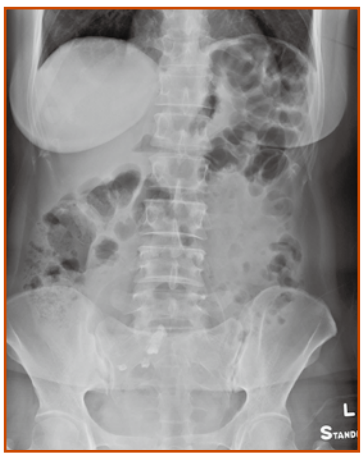
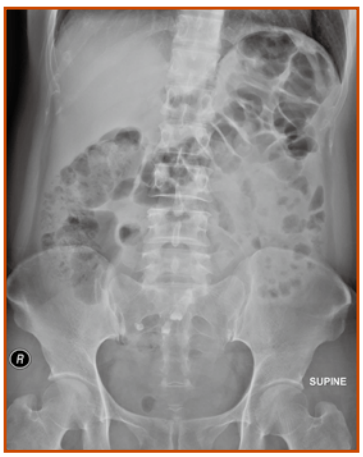
Dr John Yuen-hei MAK





A 37-year-old female presented with acute left lower quadrant abdominal pain and vomiting. There were tenderness and guarding at the left lower quadrant of the abdomen on physical examination, low grade fever with mildly elevated white cell count on blood testing. An abdominal radiograph was performed.

Questions

1. What is the abnormality on the radiograph?
2. What are the most likely differential diagnoses?
3. What is the next step of the investigation?

(See P.44 for answers)

For your adult patients with lower-risk MDS- or β-thalassemia†–associated anemia*

BRING ERYTHROID MATURATION TO LIFE

With REBLOZYL® (luspatercept), the first erythroid maturation agent, you can reduce patients' RBC transfusion burden.[1,2]

LOW-RISK MDS*

A SIGNIFICANT INCREASE IN TRANSFUSION INDEPENDENCE WITH REBLOZYL®[1]

PRIMARY ENDPOINT—
TRANSFUSION INDEPENDENCE FOR AT LEAST 8 WEEKS DURING WEEKS 1-24[1]

*Adult patients with transfusion-dependent anaemia due to very low-, low- and intermediate-risk MDS.

†Adult patients with transfusion-dependent anaemia associated with β-thalassemia.

REBLOZYL® was studied in the pivotal phase 3 MEDALIST trial of 229 patients with IPSS-R very low-, low-, or intermediate-risk MDS who have ring sideroblasts and require RBC transfusions (≥2 RBC units/8 weeks) who were randomized 2:1 to REBLOZYL® (n = 153) or placebo (n = 76). Patients were required to have had an inadequate response to prior treatment with an ESA, be intolerant of ESAs, or be ineligible for ESAs (serum EPO >200 U/L). MEDALIST excluded patients with deletion 5q MDS, white blood cell count >13 Gi/L, neutrophils <0.5 Gi/L, platelets <50 Gi/L, or with prior use of a disease-modifying agent for treatment of MDS. REBLOZYL® was administered 1 mg/kg subcutaneously every 3 weeks. Two dose-level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg) if the patient had an RBC transfusion within the prior 6 weeks. All patients received best supportive care, which included RBC transfusions as needed.[3]

REBLOZYL® was studied in a pivotal phase 3 BELIEVE trial of 336 adult patients with β-thalassemia requiring regular RBC transfusions (6–20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period who were randomized 2:1 to REBLOZYL® (n = 224) or placebo (n = 112). In BELIEVE, REBLOZYL® was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. Patients were able to receive BSC as needed, including: RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and nutritional support. The exclusion criteria for this trial included HbS/β-thalassemia or α-thalassemia, major organ damage (liver, heart, or lung disease, or renal insufficiency); recent deep vein thrombosis or stroke; or recent use of ESA, immunosuppressant, or hydroxyurea therapy.[4]

BSC=best supportive care; EPO=erythropoietin; ESA=erythropoiesis-stimulating agent; HbS=hemoglobin S; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome; RBC=red blood cell.

References:
1. Reblozyl® (luspatercept) Hong Kong Prescribing Information version September 2021. **2.** Kang C, Syed YY. Luspatercept: A Review in Transfusion-Dependent Anaemia due to Myelodysplastic Syndromes or β-Thalassaemia. Drugs. 2021;81(8):945-952. **3.** Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020;382:140-151. **4.** Cappellini MD, Viprakasit V, Taher AT, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med. 2020;382(13):1219-1231.

Reblozyl®
(luspatercept)

β-THALASSEMIA†

REBLOZYL® SIGNIFICANTLY REDUCES RBC TRANSFUSION BURDEN[1]

EXPLORATORY ENDPOINT—
≥33% REDUCTION IN TRANSFUSION BURDEN COMPARED TO BASELINE OVER ANY CONSECUTIVE 12-WEEK PERIOD[1]

ACTIVE INGREDIENT: Each vial contains 25 mg or 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept. **INDICATIONS:** Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anaemia associated with beta thalassaemia. Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia. **DOSAGE & ADMINISTRATION:** *Myelodysplastic syndromes:* The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the dose should be increased to 1.75 mg/kg. The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. *β-thalassaemia:* The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after ≥ 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg. The dose should not be increased beyond the maximum dose of 1.25 mg/kg every 3 weeks. Method of administration: For subcutaneous use. After reconstitution, Reblozyl solution should be injected subcutaneously into the upper arm, thigh or abdomen. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Pregnancy. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Thromboembolic events: In β-thalassaemia patients, thromboembolic events (TEEs) were reported in 3.6% (8/223) of patients treated with luspatercept in a controlled clinical study. Reported TEEs included deep vein thrombosis (DVT), portal vein thrombosis, pulmonary emboli and ischaemic stroke. All patients with TEEs were splenectomised and had at least one other risk factor for developing TEE (e.g. history of thrombocytosis or concomitant use of hormone replacement therapy). The occurrence of TEE was not correlated with elevated Hb levels. Increased blood pressure: In controlled clinical studies in MDS and β-thalassaemia, patients treated with luspatercept had an average increase in systolic and diastolic blood pressure of 5 mmHg from baseline. Blood pressure should be monitored prior to each luspatercept administration. In case of persistent hypertension or exacerbations of pre-existing hypertension, patients should be treated for hypertension as per current clinical guidelines. Sodium content: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'. **INTERACTIONS:** No formal clinical interaction studies have been performed. **FERTILITY, PREGNANCY & LACTATION:** The effect of luspatercept on fertility in humans is unknown. Women of childbearing potential have to use effective contraception during treatment with Reblozyl and for at least 3 months after the last dose. Prior to starting treatment with Reblozyl, a pregnancy test has to be performed for women of childbearing potential. Treatment with Reblozyl should not be started if the woman is pregnant. Because of the unknown adverse effects of luspatercept in newborns/infants, a decision must be made whether to discontinue breast-feeding during therapy with Reblozyl and for 3 months after the last dose or to discontinue Reblozyl therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **ADVERSE REACTIONS:** *Myelodysplastic syndromes:* The most frequently reported adverse drug reactions in patients receiving Reblozyl were fatigue, diarrhoea, asthenia, nausea, dizziness, back pain and headache. The most commonly reported Grade 3 or higher adverse drug reactions included syncope/presyncope, fatigue, hypertension and asthenia. The most commonly reported serious adverse drug reactions were urinary tract infection, back pain and syncope. *β-thalassaemia:* The most frequently reported adverse drug reactions in patients receiving Reblozyl were headache, bone pain and arthralgia. The most commonly reported Grade 3 or higher adverse drug reaction was hyperuricaemia. The most serious adverse reactions reported included thromboembolic events of deep vein thrombosis, ischaemic stroke portal vein thrombosis and pulmonary embolism.

Please refer to the full prescribing information before prescribing. Prescribing information is available on request.

Date of revision of the text: September 2021

2007-HK-2200020 Nov/2022

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Allogeneic Haematopoietic Stem Cell Transplantation

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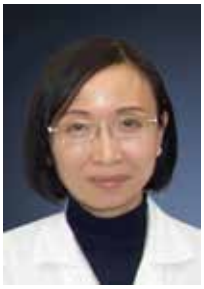

Dr Garret MK LEUNG Dr Joycelyn PY SIM

INTRODUCTION

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is considered the only curative treatment of choice for many high-risk haematological malignancies. It can be seen as an effective form of immunotherapy applied systematically against leukaemia. In addition to the cytotoxic effect of the high-dose pre-transplantation conditioning chemotherapy, the donor-derived stem cells provide allo-immunity that enables a graft-versus-tumour (GVT) effect to eradicate residual disease and prevent relapse. Along with the introduction of the various novel agents, many would have expected allo-HSCT to become a "sunset industry". Instead, the annual number of allo-HSCT has continued to increase worldwide in the past decade.[1-3] Here we shall review the development of allo-HSCT with emphasis on recent new advances and the current situation of allo-HSCT in Hong Kong.

TRENDS IN ALLO-HSCT IN THE PAST 50 YEARS

The first allo-HSCT was pioneered by the 1990 Nobel laureate, Dr E. Donnall Thomas, and reported in the New England Journal of Medicine on September 12, 1957. In the beginning, access to allo-HSCT was limited. This was due to the high transplant-related mortality (TRM) secondary to the high-dose conditioning chemo-radiotherapy, the risks of life-threatening infections and bleeding during the cytopenic phase, and the limited treatment strategies for severe graft-versus-host disease. Donor availability was another issue as only patients with a human leukocyte antigen (HLA)-matched sibling could undergo this treatment.

A comparison of transplantations performed over the last two decades would show that survival in allo-HSCT recipients have improved across all age spectra.[3] There has been significant improvement in the field of transplantation over the last 50 years, attributable to the introduction of the less toxic reduced-intensity conditioning (RIC), the improved supportive care including more potent antimicrobial agents and better transfusion support, and the newly available FDA-approved drug treatments for both acute and chronic graft-versus-host disease (GVHD). The introduction of unrelated donor and cord blood transplantations, and the subsequent establishment of the international unrelated donor registries and cord blood banks have significantly increased donor availability and have allowed patients who do not have any HLA-matched sibling to benefit from this treatment. All these advancements have led to a dramatic increase in the number of allo-HSCT, especially among "silver hair" patients who were once considered ineligible. According to the CIBMTR database, only 48 patients, representing 2% of all allo-HSCT performed in the year 2000, were aged > 65 years. In 2019, the number of allo-HSCT recipients aged > 65 years had grown to 1,888 patients, representing 26% of the total number of allo-HSCT performed in 2019. Given that the average age of diagnosis of acute myeloid leukaemia (AML), a blood malignancy which is the most common indication for allo-HSCT, is 68 years of age, this advancement has greatly improved the prognosis of the "silver hair" AML patients.[4]

WHAT IS NEW IN ALLO-HSCT OVER THE LAST DECADE?

Donor availability remains one of the major challenges to the success of allo-HSCT. Only about a quarter of the patients who need the transplant can find an HLA-identical sibling donor. Despite the expansion of the worldwide unrelated donor programme, the complicated search process for an unrelated donor necessitates 4 - 6 months of lag time from initiation of a search to the actual donation of stem cells. Unrelated cord blood as an alternative donor source offers the advantages of easy procurement and immediate availability; the low cell content poses engraftment problems for transplantation in adult patients.

WHY HAPLOIDENTICAL, THE EARLY FAILURES, THE BARRIERS, AND THE SOLUTIONS

In contrast, almost all patients who need an HSCT would have at least one identifiable haploidentical donor within his family, nuclear or extended. Biological children, parents, siblings, and frequently even more distant family members who share one haplotype are potentially qualified as donors (Fig. 1). In addition, these donors are often highly motivated and readily willing to adjust their own life plans in order to accommodate to patients' transplant schedule and changes in clinical conditions.

Yet, because of the increased T-cell mediated allo-reactivity, the early development of haploidentical HSCT (haplo-HSCT) was hindered by the high rates of GVHD and graft failure, resulting in ~10% long-term survival.[5]

By removing the T-cells from the graft, Reisner and colleagues performed the first successful haplo-HSCT in children with severe combined immunodeficiency (SCID) using T-cell depleted (TCD) haploidentical

grafts.[6] However, the same approach was not applicable to other non-SCID patients, in whom the underlying immune system is generally functional, and a high rate of graft failure due to the unopposed host versus graft (HVG) rejection.

This limitation was later overcome by the use of T-cell depleted (TCD) "megadose" stem cell grafts (containing ~10×106/kg CD34 + haematopoietic stem cells). Although the "megadose" TCD approach was able to improve the primary engraftment rate to > 90% with comparable GVHD rate as HLA-matched transplants, there was a high non-relapse mortality of > 30% observed across studies, largely owing to post-transplant infections and primary disease relapse. As a result, the 2-year event-free survival probability was only ~40 - 50%.

The ultimate breakthrough that led to the widespread use of haplo-HSCT, including in resource-restricted countries, was the introduction of the "post-transplant cyclophosphamide" (PTCy)-based haploidentical transplantation using a T-cell replete (TCR, i.e., non-T-cell depleted) stem cell graft. This immunological effect of PTCy was first observed in the 1960s in animal models of allogeneic skin grafts whereby cyclophosphamide administration within a window of up to 4 days after grafting delayed rejection.[7] It was thought that the PTCy exerts selective deletion of the alloreactive T cells. However, more recent work by Kanakry and colleagues in dedicated murine models suggested that the PTCy mediates its effects through the preferential recovery and expansion of regulatory T cells after PTCy.[8]

Pioneered by the Johns Hopkins group, the first clinical study of unmanipulated haplo-HCT was performed using non-myeloablative conditioning and one dose of PTCy at 50 mg/kg on day +3. The post-transplant PTCy immunosuppressive regimen included mycophenolate mofetil and tacrolimus starting on day +4 in 13 patients (Fig. 2A).[9] Subsequent prospective clinical trials, administering two doses of PTCy on days +3 and +4, demonstrated a trend towards a higher engraftment and a lower risk of extensive chronic GVHD, which has later become the current standard PTCy protocol.

Another TCR haplo-HSCT commonly used is the GIAC approach pioneered by the Peking University People's Hospital (PUPH) group (Fig. 2B).[10] This approach uses Antihuman Thymocyte Immunoglobulin (ATG) part of the conditioning regimen to overcome the allo-reactivity across the HLA barrier. Owing to its long half-life, ATG exerts a dual effect on both recipient T cells and donor T cells, and therefore facilitating engraftment and preventing GVHD at the same time. The stem cell graft used in the GIAC protocol consists of a combination of G-CSF-primed bone marrow and PBSC. The combination of both marrow and stem cell graft allows a higher CD34+ cells from the PBSC graft that promote engraftment and decrease relapse. In addition, by virtue of inducing differences in cytokine milieu, T-cell polarisation and T-cell hypo-responsiveness, the GCSF-primed bone marrow leads to less acute and chronic GVHD. In the initial study of 171 patients using GIAC, most of whom had acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), or chronic myeloid leukaemia (CML), all patients achieved engraftment with sustained full donor chimerism. The rates of leukaemia-free survival and cumulative incidences of grade II-IV acute GVHD and extensive chronic GVHD were comparable to other conventional alternative donor allo-HSCT.

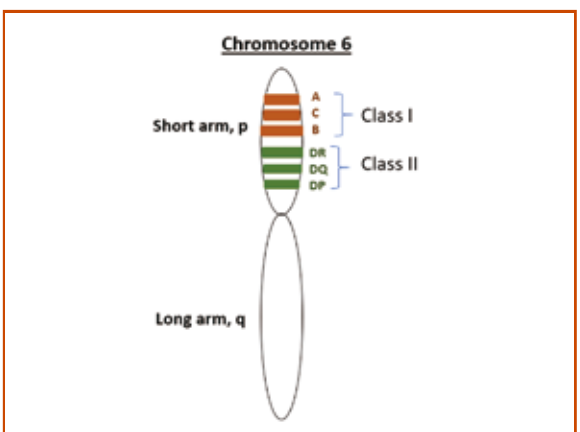

Fig. 1A. Distribution of HLA alleles on chromosome 6. (Figure Developed by the authors)

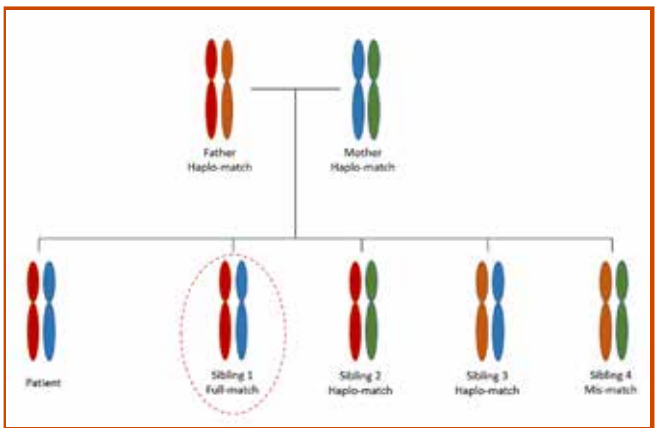

Fig. 1B. A representative inheritance pattern of HLA alleles in a family of 7 members. Each sibling has a 25% chance of being a full match based on inheritance of the same maternal and paternal alleles as the patient. (Figure developed by the authors)

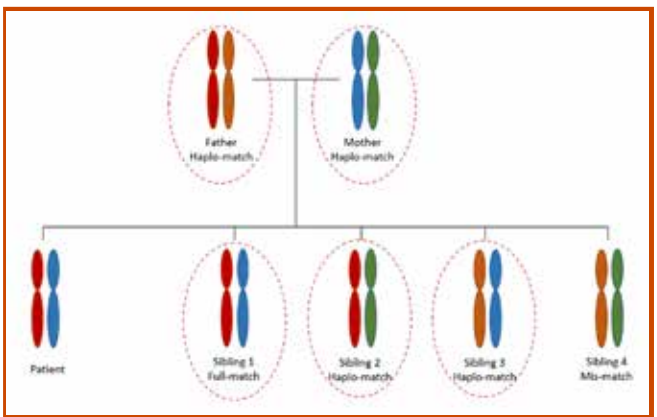

Fig. 1C. A representative inheritance pattern of HLA alleles in the same family as in Figure 1B. Each sibling has a 50% chance of being a haploidentical match by virtue of having inherited one identical allele from the parents. Both parents are haploidentical match to patient. (Figure developed by the authors)

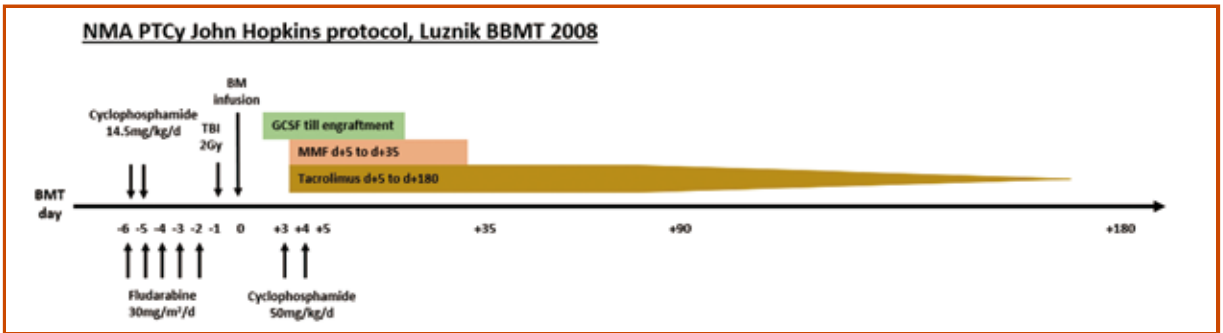

Fig. 2A. Non-myeloablative (NMA) PTCy Hopkins protocol (Adapted from Luznik BBMT 2008[9]).

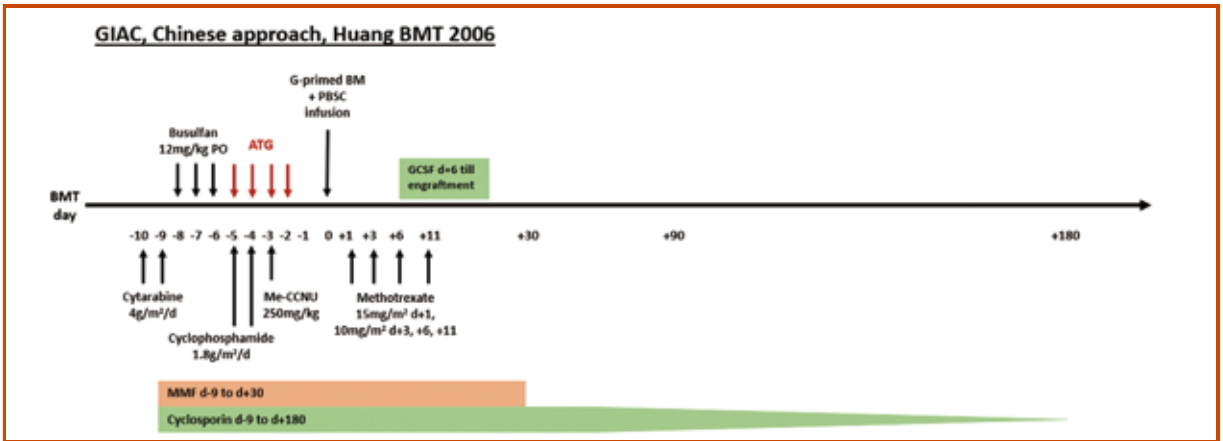

Fig. 2B. GIAC protocol, Chinese approach (Adapted from Huang BMT 2006[10]) Click or tap here to enter text. GIAC stands for: Granulocyte colony-stimulating factor mobilisation; Intensified immunologic suppression; Antihuman thymocyte immunoglobulin (ATG); Combined use of bone marrow and peripheral blood as the graft.

Allo-HSCT in Hong Kong

Queen Mary Hospital (QMH) is the only adult allo-HSCT centre in Hong Kong. Lie et al. described the landscape of HSCT in Hong Kong in 2009, including 1708 HSCT performed at QMH during the period 1990 to 2008.[11] Adult recipients accounted for 85.8%, and allo-HSCT accounted for 66%. Acute myeloid leukaemia (AML) was the most common indication for adult HSCT, followed by chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) (Table 1). The main donor source was matched sibling at the beginning, with a gradual increase in the number of unrelated donor transplants to about one-third of all allo-HSCT by 2008.

Table 1. Top five indications for allogeneic HSCT in Hong Kong (Personal data of the authors)

	1990-2009*	2012-2021
Acute myeloid leukaemia	24%	43%
Chronic myeloid leukaemia	19%	5%
Acute lymphoblastic leukaemia	12%	25%
Myelodysplastic syndrome/ myeloproliferative neoplasm	7%	13%
Non-Hodgkin's lymphoma	6%	8%

*Derived from Lie HKMJ 2009.11

A decade on, there have been significant changes in the HSCT practice. Among 893 adult patients who underwent allo-HSCT at QMH during the period 2012 to 2021, AML remained the most common indication (N=388, 43%), followed by ALL (N=221, 25%), then myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) (N=119, 13%) (Fig. 3). Only 5% of patients had allo-HSCT for chronic myeloid leukaemia (CML) as tyrosine kinase inhibitors have become the standard of care since the introduction of imatinib.

We have also observed an increase in the age at which patients received their first transplantation (Fig. 4). Omitting the 16.6% of patients aged < 20 years in the Lie study, the median age-group at transplantation (including auto-HSCT) was 40-49 years, as compared to 50-59 years in the current study accounting for 39% of all allo-HSCT performed during this period. This change can be attributed to the introduction of the less toxic reduced-intensity conditioning to patients deemed unfit for the more toxic conventional myeloablative conditioning.

Another major change observed is the increasing use of haplo-identical donor transplantation. Matched sibling and unrelated donors were the main donor source for our patients before 2014.[11] QMH started our adult Haplo-HSCT programme in 2014. The option was offered to patients with high-risk diseases yet lacking suitable matched related or unrelated donors. The haploidentical donor has proven to be a valuable donor source for HSCT during the COVID outbreak. The number of haplo-HSCT even surpassed that of sibling and unrelated HSCT in 2021 (Fig. 5).

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* Time of follow-up varies for different indications regarding respective study: CLL – 96.6 months (Maximum)[2]; R/R CLL – 71.6 months (Maximum)[3] ; R/R MCL – 9.7 years (Maximum)[1]; R/R WM – 61 months (Maximum)[4]
† Monotherapy or combination therapy with rituximab or obinutuzumab.[5] Median PFS – 82.1 months-not estimable.[2]
‡ Monotherapy or combination therapy with bendamustine and rituximab.[5] Median PFS – 44.1 months[3]
§ Monotherapy.[5] Median PFS – 12.5 months[1]
¶ Monotherapy.[5] Median PFS – 39 months[4]

BTKi = Bruton's tyrosine kinase inhibitor. CLL = chronic lymphocytic leukaemia. R/R CLL = relapsed or refractory chronic lymphocytic leukaemia. R/R MCL = relapsed or refractory mantle cell lymphoma. R/R WM = relapsed or refractory Waldenström's macroglobulinaemia.

References: 1. Dreyling M, et al. HemaSphere. 2022; 6(5):e712. 2. Barr PM, et al. Blood Adv. 2022; 6(11):3440-3450. 3. Munir T, et al. Am J Hematol. 2019; 94(12):1353-1363. 4. Trotman J, et al. Clin Cancer Res. 2021; 27(21):5793-5800 5. IMBRUVICA® Tablet Hong Kong Prescribing Information P01.

Imbruvica® Tablets 140mg
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Ibrutinib
INDICATION(S): Imbruvica as a single agent indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). As a single agent or in combination with rituximab or obinutuzumab indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). As a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. As a single agent indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. In combination with rituximab indicated for the treatment of adult patients with WM. **DOSAGE & ADMINISTRATION:** MCL: 560 mg once daily; CLL and WM: either as a single agent or in combination, 420 mg once daily. Recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day. Swallow whole with water. Do not take with grapefruit juice or Seville oranges. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of its excipients. Use of preparations containing St. John's Wort is contraindicated in patients treated with IMBRUVICA. **SPECIAL WARNINGS & PRECAUTIONS:** Bleeding-related events: There have been reports of bleeding events in patients treated with IMBRUVICA, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae, and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial haemorrhage, and haematuria. Warfarin or other vitamin K antagonists should not be administered concomitantly. Avoid supplements such as fish oil and vitamin E preparations. IMBRUVICA should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. Leukostasis: Consider temporarily withholding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated. Splenic rupture: Monitor disease status and spleen size when IMBRUVICA treatment is interrupted or ceased. Infections: Patients should be monitored for fever, abnormal liver function tests, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Physicians should consider progressive multifocal leukoencephalopathy (PML) in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. Appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. Cytopenias: Monitor complete blood counts monthly. Interstitial Lung Disease (ILD): Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt IMBRUVICA and manage ILD appropriately. Cardiac arrhythmia and cardiac failure: Periodically monitor all patients clinically for cardiac manifestations. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed. In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, temporarily discontinue IMBRUVICA and perform a thorough clinical benefit/risk assessment before possibly restarting therapy. In patients at high risk for atrial fibrillation and where alternatives to IMBRUVICA are non-suitable, consider tightly controlled treatment with anticoagulants. Monitor patients for signs and symptoms of cardiac failure. Cerebrovascular accidents: Monitor patients regularly. Tumour lysis syndrome: Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions. Non-melanoma skin cancer: Monitor patients for the appearance of non-melanoma skin cancer. Viral reactivation: Hepatitis B virus (HBV) status should be established before initiating treatment with IMBRUVICA. Consult physician with expertise in treatment of hepatitis B for patients tested positive for HBV infection. Consult liver disease expert before initiating IMBRUVICA treatment for patients with positive hepatitis B serology. Monitor and manage patients following local medical standards to prevent hepatitis B reactivation. Hypertension: Regularly monitor blood pressure in patients and initiate or adjust antihypertensive medication as appropriate. Haemophagocytic lymphohistiocytosis (HLH): Patients should be informed about symptoms of HLH. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. Drug-drug interactions: Patients should be closely monitored for signs of IMBRUVICA toxicity if a CYP3A4 inhibitor must be used. If a CYP3A4 inducer must be used, closely monitor patients for signs of IMBRUVICA lack of efficacy. **SIDE EFFECTS:** Diarrhoea, neutropenia, musculoskeletal pain, rash, haemorrhage, thrombocytopenia, nausea, pyrexia, arthralgia, and upper respiratory tract infection Refer to the full prescribing information for other side effects. **PREGNANCY & LACTATION:** Women of childbearing potential must use a highly effective method of contraception while taking IMBRUVICA and for three months after stopping treatment. Imbruvica should not be used during pregnancy. Breast feeding should be discontinued during treatment with IMBRUVICA. **INTERACTIONS:** Avoid co-administration with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers. If a moderate CYP3A4 inhibitor must be used, reduce IMBRUVICA dose. Monitor patient closely for toxicity and follow dose modification guidance as needed.
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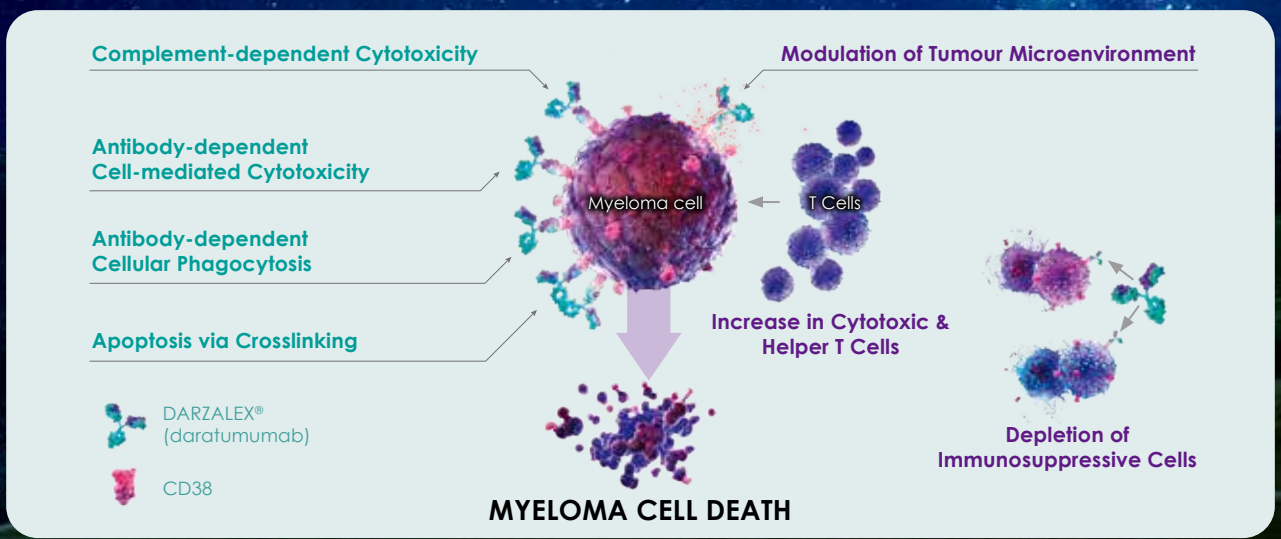

DARZALEX® (daratumumab) is indicated[2]:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

See **DARZALEX®** prescribing information for full indication, including its use as a monotherapy[2].

References:
1. Sanchez L, Wang Y, Siegel DS, and Wang ML. Daratumumab: a first-in-class CD38 monoclonal antibody for the treatment of multiple myeloma. J Hematol Oncol. 2016; 9: 51. 2. DARZALEX® Hong Kong prescribing information P06. 3. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186:1840-1848. 4. Overdijk MB, Verploegen S, Bögels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7:311-321. 5. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016;128:384-394.

Darzalex® Concentrate for Solution for Infusion 100mg/5mL, 400mg/20mL
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): daratumumab
INDICATION(S): DARZALEX is indicated: • in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. • in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. • in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. • as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. DOSAGE & ADMINISTRATION: Intravenous (IV) infusion only following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. DARZALEX dosing schedule - In combination with lenalidomide (4-week cycle regimen) and for monotherapy: 16 mg/kg body weight given weekly from weeks 1 to weeks 8, then every 2 weeks from weeks 9 to 24 and every 4 weeks from week 25 onwards until disease progression. In combination with bortezomib, melphalan and prednisone (6-week cycle dosing regimen): 16 mg/kg body weight, given weekly from weeks 1 to week 6, and then every 3 weeks for week 7 to 54 and every 4 weeks from week 55 onwards until disease progression. Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by once weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. In combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT): 16 mg/kg body weight given weekly for induction from weeks 1 – 8, followed by every 2 weeks from weeks 9 – 16, and stop for high dose chemotherapy and ASCT. For consolidation, every 2 weeks from weeks 1 to 8. In combination with bortezomib (3-week cycle regimen): 16 mg/kg body weight, given once a week for the first 9 weeks. From week 10 to 24, DARZALEX is given every 3 weeks, and then every 4 weeks from week 25 onwards until disease progression. Pre- and post-infusion medicinal products should be administered to reduce the risk of infusion-related reactions. To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively. CONTRAINDICATIONS: Known hypersensitivity to the active substance or to any of the excipients in the DARZALEX formulation. SPECIAL WARNINGS & PRECAUTIONS: Infusion-related reactions (IRRs): DARZALEX can cause serious infusion related reactions (IRRs), including anaphylactic reactions. Monitor all patients throughout the infusion for IRRs. Monitor post-infusion until symptoms resolve for patients experience any Grade IRRs. Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior treatment. Reduce infusion rate when re-starting infusion for patients with Grade 1,2 or 3 IRRs. If anaphylactic reaction or life-threatening (Grade 4) infusion reaction occurs, initiate appropriate emergency resuscitation immediately and discontinue DARZALEX therapy immediately and permanently. Neutropenia/Thrombocytopenia: DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment and monitor patients with neutropenia for signs of infection. Interference with indirect antiglobulin test (indirect Coombs test): Daratumumab binds to CD38 found at low levels on red blood cells and may result in a positive indirect Coombs test. Patients should be typed and screened prior to starting daratumumab treatment. In event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests. Interference with determination of complete response: Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis and immunofixation assays used for clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein. Hepatitis B virus (HBV) reactivation: Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment. For patients with evidence of positive HBV serology, monitor signs of HBV reactivation during, and for at least six months following the end of treatment. In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and institute appropriate treatment. Excipients: Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively. This corresponds to 0.46% and 1.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult, respectively. SIDE EFFECTS: Most frequent adverse reactions: IRR, fatigue, nausea, diarrhoea, constipation, pyrexia, dyspnoea, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, asthenia, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions: sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation. Refer to the full prescribing information for other side effects. PREGNANCY & LACTATION: Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment. Daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. INTERACTIONS: Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes. Interference with indirect antiglobulin test (indirect Coombs test): Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol to disrupt daratumumab binding or other locally validated methods or consider phenotyping/genotyping. Interference with serum protein electrophoresis and immunofixation tests: consider using validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum for suspected daratumumab interference.
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Up until 30 June 2022, a total of 132 adult haplo-HSCT have been performed at QMH. The median age of the HSCT cohort was 48 years (range, 20-66 years). AML and high-risk MDS/MPN again accounted for the majority (55%) of the cohort, followed by ALL (40%), relapsed lymphoma (14%) and CML (3%). Fifty-six percent were in second remission or accelerated phase/blastic crisis, or had active disease or high-risk MDS/MPN at the time of HSCT. Seventeen patients underwent their second transplantation, and two patients their third. Parents were the donors in 24% of haplo-HSCT, haploidentical siblings in 35%, and children in 41%. One patient received haematopoietic stem cells from his nephew.

With a median follow-up of 423 days (range, 42-2049 days) among 95 surviving patients, the 1-year progression-free survival (PFS) and overall survival (OS) were 61% and 77%, respectively (Fig. 6). The main cause of death was post-transplant relapse of the primary haematological disease, accounting for 61% of mortality in the cohort.

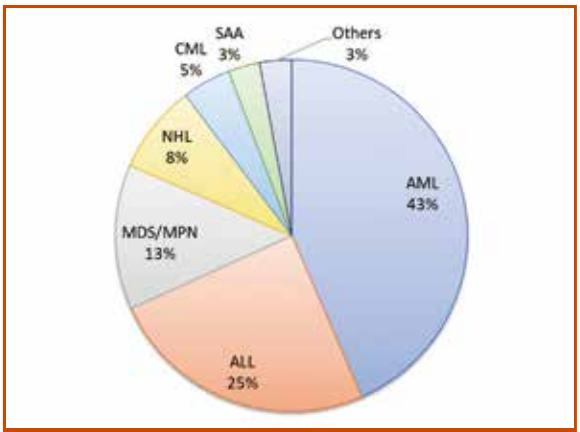

Fig. 3. Allogeneic HSCT performed at Queen Mary Hospital from 2012 to 2021. AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm; NHL, non-Hodgkin's lymphoma; CML, chronic myelogenous leukaemia; SAA, severe aplastic anaemia; others, including multiple myeloma, Hodgkin's lymphoma and other leukaemias. (Personal data of the authors)

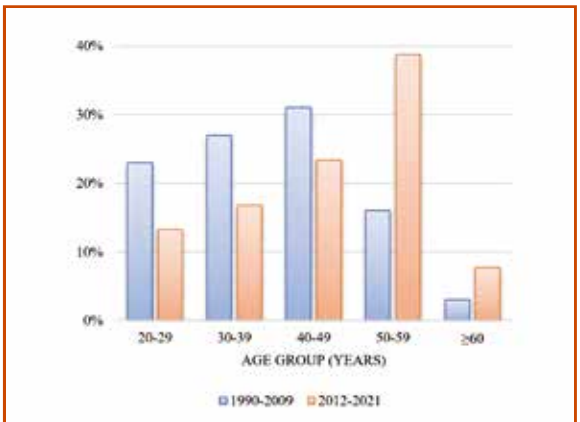

Fig. 4. Comparison of HSCT recipients' age at HSCT. (Personal data of the authors)

Fig. 5. Donor types for allo-HSCT at QMH during the period 2012 to 2021. (Personal data of the authors)

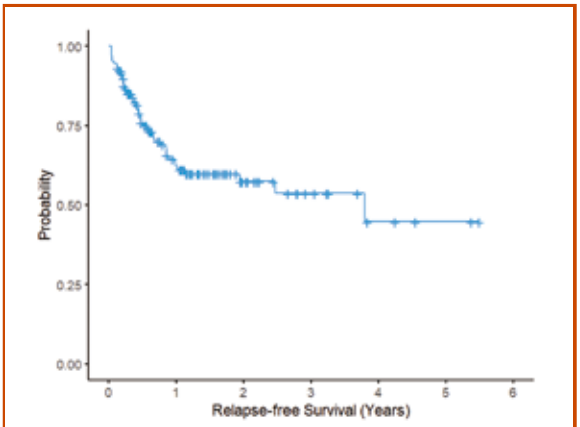

Fig. 6A. Progression-free survival among the first 132 adult patients who underwent haploidentical HSCT at QMH. (Personal data of the authors)

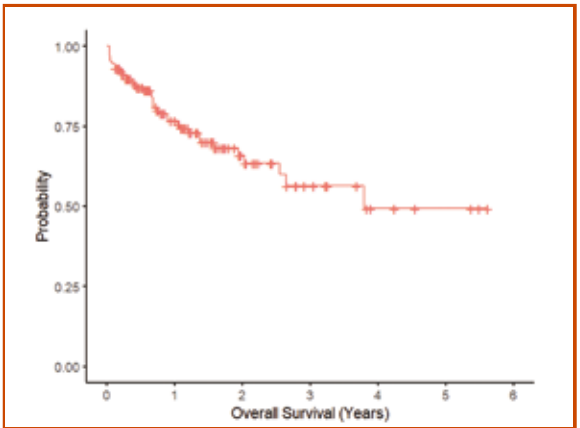

Fig. 6B. Overall survival among the first 132 adult patients who underwent haploidentical HSCT at QMH. (Personal data of the authors)

CONCLUSION

Despite the many advancements in the field of allogeneic haematopoietic stem cell transplantation we have made during the past 50 years, many challenges remain. With the less toxic reduced-intensity conditioning and the improved supportive care, allo-HSCT is now a much safer treatment option than we first started. On the other hand, relapse of primary disease emerged as the major cause of failure after allo-HSCT (a topic not covered here). Methods of manipulating the graft immune activity to maximise GVL and minimise GVHD will be a new direction which could promote the next breakthrough in allo-HSCT. Novel agents likely serve to complement and build on the immunological GVL platform set up by allo-HSCT, rather than replacing it.

In a survey conducted in United States, transplantation physicians predicted a continued increase in the number of HSCTs performed for malignant as well as benign diseases such as sickle cell disease, autoimmune and genetic disorders in 2023.[12] While the majority (63%) predicted that matched related donors will remain the preferred donor source for adult HSCT recipients, haploidentical donor (21%) ranked second and matched unrelated donor (17%) third as their primary preferred donor source.[13] Indeed, haploidentical donor HSCT has become the most common transplant type in Europe and China in 2016.[2,13] It appears that allo-HSCT will remain an important weapon in our battle against haematological malignancies in the years to come.

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References :
1. L. Pradelli et al. Clinical Nutrition 33 (2014) 785-792
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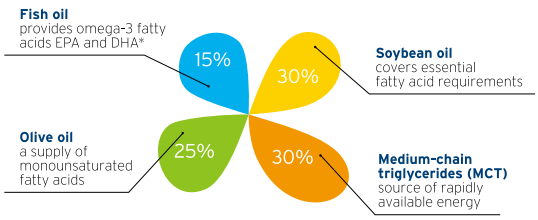

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HK-DA-266-2021

Immunotherapies for Haematological Malignancies Chimeric Antigen Receptor T-cell (CAR-T cell) Therapy

Dr Thomas SY CHAN

MBBS(HK), FRCP(Edin), FHKAM(Medicine)

Consultant, Division of Haematology and Haematopoietic Stem Cell Transplant, Department of Medicine, Queen Mary Hospital

Dr Thomas SY CHAN

INTRODUCTION

In the last decade, immunotherapy has emerged as a breakthrough in cancer therapeutics.[1] Among all cancers, haematological malignancies are particularly susceptible to manipulation of the immune system because of several reasons: (i) the immune effector cells are usually in constant contact with the malignant cells, allowing maximal interaction between the two parties; (ii) the normal counterparts of the malignant blood cells are often antigen-presenting in nature and are thus more immunogenic; and (iii) the expression of surface molecules in the malignant cells is relatively unique, making these molecules good targets for immunological attack without sacrificing organ function.[2] There are many ways in which the immune system can be harnessed to control blood cancers. Readers can also refer to the other articles of this issue. In the present article, I will focus on the latest form of cell-based immunotherapy, chimeric antigen receptor T-cell (CAR-T cell) therapy.

Cell-based immunotherapy involves modification or transferal of immune cells to fight against cancer cells. Chimeric antigen receptor T cell (CAR-T) therapy is the most successful form of cell-based immunotherapy to date. Autologous or allogeneic T lymphocytes are genetically engineered to express chimeric antigen receptors (CARs), targeting the antigens expressed on the tumour cell surface. CARs are synthetic transmembrane proteins designed to activate T lymphocytes, resulting in tumour cell cytotoxicity independent of human leucocyte antigen (HLA). A CAR consists of three parts, an ectodomain responsible for antigen recognition, a transmembrane domain, and an intracellular domain responsible for intracellular signalling. An ectodomain is usually formed from a single chain variable fragment (scfv), which is a fusion protein of the variable region of the heavy and light chains of an antibody. While the intracellular domain of the first-generation CAR contains CD3-zeta for T lymphocyte activation, this signal alone is insufficient for proliferation, leading to short in vivo persistence of CAR-T. In the second and subsequent generations of CAR, co-stimulatory proteins are built together with CD3-zeta, which substantially improves CAR-T cell proliferation and persistence after infusion.[3]

The manufacturing process of CAR-T cells is complex and labour-intensive (Fig. 1).[4] T-lymphocytes are collected from the patient's blood through leucopheresis. The harvested cells are then activated in vitro. Next, the CAR transgene will be introduced into the T-lymphocyte genome (typically through viral transduction). Further expansion of T-lymphocytes in vitro is performed before infusion to patients.

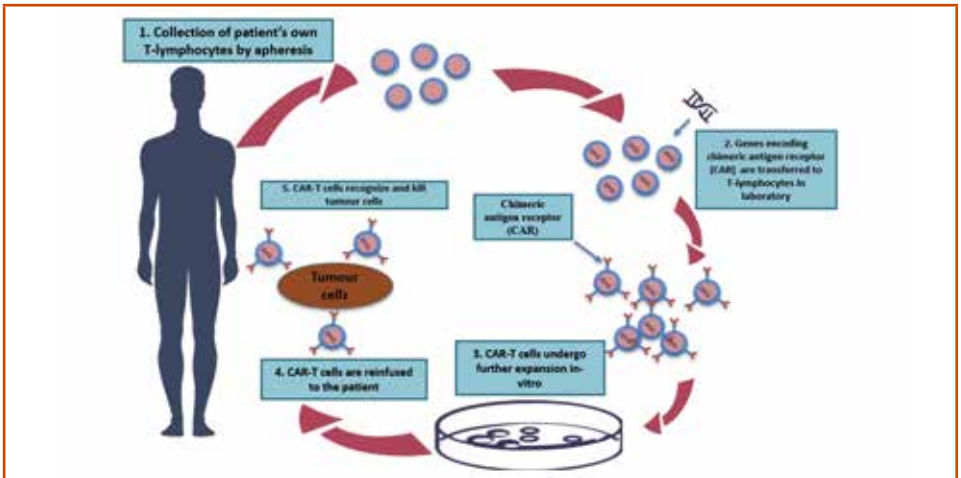

***Fig. 1**: Brief outline of the steps involved in CAR-T therapy (Created by author)*
Step 1. T-lymphocytes are harvested from the patient's blood through apheresis.
Step 2. T-lymphocytes undergo genetic medication where CAR gene is inserted into their genome, leading to the expression of CAR protein on their surface
Step 3. CAR-T cells undergo further expansion
Step 4. CAR-T cells are re-infused into the patient
Step 5. CAR-T cells undergo further in-vivo expansion and exercise tumour cell killing

Guidelines of current good manufacturing practice (GMP) should be closely followed regarding the safety, purity and potency of the final product. Depending on the specific product, the manufacturing process takes two to four weeks to complete, during which the patient may need bridging chemotherapy/radiotherapy to control the disease before the infusion of CAR-T cells. The typical cell dose delivered is in the range of 10^6 CAR-T cells per kg body weight.

There are currently six CAR-T products approved by the United States Food and Drug Administration (FDA): Tisagenlecleucel (Tisa-cel, for treatment of relapsed or refractory (R/R) B-acute lymphoblastic leukaemia (B-ALL), large B-cell lymphoma and follicular lymphoma), Axicabtagene Ciloleucel (Axi-cel, for treatment of R/R large B-cell lymphoma), Brexucabtagene Autoleucel (Brexu-cel, for treatment of R/R B-ALL and mantle cell lymphoma (MCL)), Lisocabtagene Maraleucel (Liso-cel, for treatment of R/R large B-cell lymphoma and follicular lymphoma), Idecabtagene Vicleucel (Ide-cel, for treatment of R/R multiple myeloma) and Ciltacabtagene Autoleucel (Cilta-cel, for treatment of R/R multiple myeloma).[5] The first four CAR-T cell products target CD19, a cell surface protein almost universally expressed on benign and malignant B-lymphocytes, while the latter two target B-cell maturation antigen (BCMA) expressed on mature plasma cells and myeloma cells.

Results from clinical trials for CAR-T treatment in different haematological malignancies are encouraging. For example, in **R/R ALL**, the complete remission (CR) rates after CAR-T cell infusion are 71% for Brexu-cel and 81% for Tisa-cel.[6,7] In Tisa-cel treated patients, around 50% are still in CR at 12 months post-infusion.[7] These patients can be considered cured as relapse beyond 12 months is rare. **In R/R large B-cell lymphoma**, the complete response rates for Tisa-cel, Axi-cel and Liso-cel were 40%, 52% and 53%, respectively.[8-10] A consistent finding among all three products in these pivotal trials for aggressive lymphoma is that roughly 30-40% of patients can achieve durable remission. **In R/R myeloma**, Ciltacabtagene Autoleucel induces a stringent complete response (sCR) in 67% of patients, and the median progression-free survival is not reached with a median follow-up time of 12.4 months.[11] Taken together, CAR-T therapy has shown a remarkable success in the treatment of R/R blood cancers, which was unachievable by contemporary chemotherapeutic regimens.

The side-effect profile of CAR-T cell therapy is different from conventional chemotherapy.[12] A few days before infusion of CAR-T cells, chemotherapy is generally given to deplete resident lymphocytes to optimise in vivo expansion of CAR-T cells after infusion. Neutropenia is, therefore, common, and patients could suffer from opportunistic infections. In addition, two important complications relatively unique to CAR-T cell therapy may occur: cytokine release syndrome (CRS) and immune effector cells associated neurotoxicity syndrome (ICANS). CRS results from massive cytokine release due to the activation and proliferation of CAR-T. Cytokines, including interleukin-6, interleukin-10 and interferon-gamma, are markedly elevated, leading to fever, vasodilatory shock, systemic capillary leak and multiple organ failure. Grade 3/4 CRS has a reported incidence of 10-40%. Treatment is aimed at dampening excessive inflammation with corticosteroid and interleukin-6 receptor antagonists (Tocilizumab). ICANS occurs because of a breakdown of the blood-brain barrier, leading to leakage of CAR-T cells and inflammatory cytokines into the central nervous system (CNS). The incidence ranges from 0-50% across different products. Manifestations of ICANS vary and can include tremors, headache, confusion, aphasia, convulsion or even coma. Management of low grade ICANS is supportive. If ICANS is severe, corticosteroids (dexamethasone) should be given to control excessive inflammation in the CNS.

Despite the high remission rate in clinical trials, some patients eventually have disease relapse. Clinical and molecular predictors may help to identify patients at a higher risk of relapse.[13,14] Re-treatment with CAR-T infusion generally has a much lower rate of success, which is likely due to immunity against the CAR molecule.[15]

CAR-T cell therapy was introduced to public hospitals in May 2021. Tisagenlecleucel is the only registered CAR-T cell product in Hong Kong and is licensed for treating R/R ALL under the age of 25 and R/R large B-cell lymphoma. At the time of writing this manuscript, Queen Mary Hospital and Hong Kong Children's Hospital are the only public hospitals treating adult and pediatric CAR-T patients, respectively. After financial assessment, eligible patients will be offered a subsidy from the Community Care Fund.

Globally, the scale of CAR-T trials is growing at an unprecedented pace. The indications for CAR-T treatment are also expanding rapidly. China is currently running the largest number of CAR-T trials, followed by the US.[16] Refinement of CAR-T manufacturing procedure, better preventive measures for complications and understanding of the pathogenesis of relapse after CAR-T will eventually make CAR-T a safer and more effective treatment strategy for haematological malignancies.

CASE PRESENTATION

A 67-year-old woman was referred for CAR-T cell therapy. She suffers from stage IV diffuse large B cell lymphoma with bone marrow involvement arising from pre-existing follicular lymphoma. She was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin), PRB (polatuzumab, rituximab and bendamustine) and BVP (bleomycin, vinblastine, cisplatin). None of these regimens resulted in a durable response. She was accepted into the CAR-T programme. She received bridging chemotherapy (R-DIME (rituximab, dexamethasone, ifosfamide, methotrexate and etoposide)) during CAR-T manufacturing. The CAR-T infusion was uneventful, and she was discharged on day 25. Figure 2 shows positron-emission-tomography/computerised tomography (PET/CT) images which were performed before (Fig. 2A) and one month after (Fig. 2B) CAR-T cells infusion, showing complete metabolic response. She is now six months post-treatment. Serial PET/CT scans showed no evidence of disease recurrence.

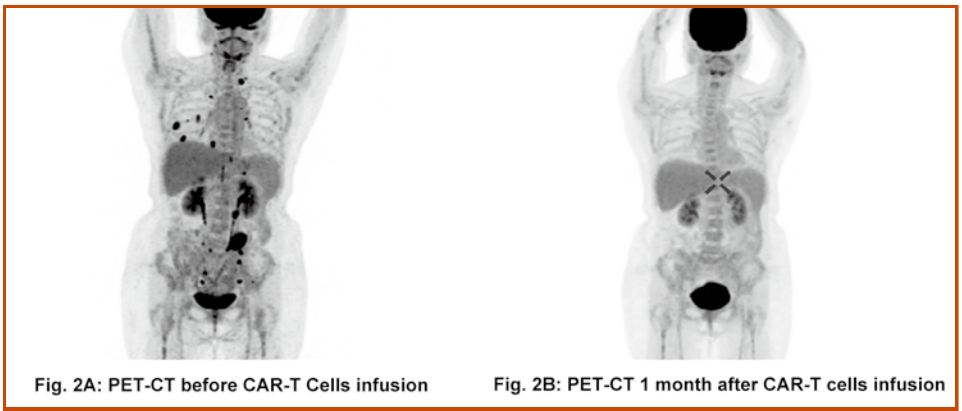

Fig. 2A: PET-CT before CAR-T Cells infusion

Fig. 2B: PET-CT 1 month after CAR-T cells infusion

Fig. 2: PET/CT scans of the patient before and after CAR-T threapy (Personal collection)

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For patients with CML or Ph+ ALL when no other TKI# is indicated, or who have the T315I mutation[2]

Abbreviated Prescribing Information

ICLUSIG® (ponatinib) 15 mg/45 mg tablets. **Indication:** In adult patients with (1) chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation; and (2) Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. **Dosage:** Recommended starting dose: 45 mg once daily. Assess the patient's cardiovascular status before treatment initiation. Refer to the package insert for dose modification for management of toxicities. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and precautions:** Risk of myelosuppression; a complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated. Monitoring for evidence of arterial occlusion and thromboembolism; interrupt treatment in such events. If decreased vision or blurred vision occurs, perform an ophthalmic examination (including fundoscopy). Reports of treatment-emergent hypertension; urgent clinical intervention required for hypertension associated with confusion, headache, chest pain, or shortness of breath. Discontinue treatment in patients developing serious heart failure. Caution recommended in patients with a history of pancreatitis or alcohol abuse. Patients with severe hypertriglyceridemia should be appropriately managed to avoid pancreatitis. Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated. Interrupt treatment and evaluate patients for serious or severe haemorrhage. Monitor for active HBV infection in HBV carriers throughout therapy and for several months after treatment. Interrupt treatment in the event of posterior reversible encephalopathy syndrome. Caution recommended in patients with hepatic/renal impairment. Not advised in pregnancy; only used when clearly necessary. Stop breastfeeding during treatment & use effective contraception during treatment. **Drug interactions:** Caution in concomitant use with CYP3A inhibitors/inducers, transporter substrates (e.g. P-gp and BCRP) & anti-clotting agents in patients who may be at risk of bleeding events. **Adverse reactions:** Pneumonia, pancreatitis, abdominal pain, atrial fibrillation, pyrexia, myocardial infarction, peripheral arterial occlusive disease, anaemia, angina pectoris, decreased platelet count, febrile neutropenia, hypertension, coronary artery disease, congestive cardiac failure, cerebrovascular accident, sepsis, cellulitis, acute kidney injury, UTI and increased lipase. **Please see full Prescribing information for details. Full prescribing information is available upon request.**

Abbreviations:
CML: chronic myeloid leukemia; Ph+ ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; TKI: tyrosine kinase inhibitor

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#: Imatinib, Nilotinib, Dasatinib

Otsuka Otsuka Pharmaceutical (H.K.) Ltd.
21/F, East Exchange Tower, 38 Leighton Road, Causeway Bay, Hong Kong. Tel: 2881 6299 Fax: 2577 5206

HKOP-ICL-202109-001

Which Type Of Watch Collector Are You?

Dr Herman SY LIU

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Specialist in Hematology and Hematological Oncology

Dr Herman SY LIU

Collecting is a hobby of gathering things for fun. Common things that people collect include coins, stamps, photographs, vinyl records, musical instruments, pens, cameras, toys, drawings, art pieces, cameras, automobiles, wines, gems and watches...and Non-fungible tokens (NFT).

In recent years, younger generations are entering into the watch game, thanks to social media. I am also aware of many watch enthusiasts within the medical profession with a wide range of collections. I take this opportunity to share some of my humble timepieces. They can be divided into the following categories:

ROLEX

I started the discussion with the brand Rolex because it is the 'King' of watch brands to many collectors, in terms of popularity. For many years, Rolex remained the leader amongst Swiss watch brands, constituting 29% of market share and an estimated turnover of CHF 8 billion in 2021, an estimation of selling 1 million watches annually.

Since it was founded in 1908, the brand has made many innovations and introduced world renowned models like Daytona, Submariner, GMT, Day-Date, Datejust…

I have chosen four timepieces of different precious metals: Yellow Gold, Rose Gold, White Gold and Platinum (Fig. 1)

(a) Left upper quadrant: **Rolex Submariner 126619LB** in white gold, introduced in 2020, nicknamed Cookie Monster. The design is faithful to the original model launched in 1953. Wearing a yellow or rose gold watch can be a statement; white gold is definitely under the radar and can be a good alternative with the same elegance and classiness.

(b) Left lower quadrant: **Rolex GMT Master II 126715CHNR** in everose gold, introduced in 2018, nicknamed Root Beer. Rolex first introduced the everose gold in 2005; the gold used in Rolex watches is 18K, which means it is 75% gold by weight. The colour variation occurs as a result of the different materials used in composing the other 25% of the alloy (copper, platinum etc.). I did not ask for this particular model, but who will turn down an offer from the authorised dealer nowadays?

(c) Right upper quadrant: **Rolex Cosmograph Daytona 116506** in platinum, introduced in 2013, to celebrate the 50th anniversary of the original chronograph. It is the first Daytona in platinum with a heft of 286 grams. The dial is of ice-blue colour, and the bezel is brown, paying homage to Paul Newman's famous blue eyes and brown hair. A keeper for sure!

(d) Right lower quadrant: **Rolex Submariner 126618LB** in yellow, introduced in 2020. I particularly like the combination of yellow gold and a royal blue dial which had been in production for many years in the submariner line. I had been in love with its predecessor since I was a medical student.

However, my daily wear is seldom precious metal Rolexes; you may see me wearing Milgauss and AirKing instead.

Fig. 1: Rolex in White Gold, Everose Gold, Yellow Gold and Platinum (Personal Collection)

THE HOLY TRINITY SPORTS WATCHES

When I used the term 'King' to describe Rolex earlier, I knew some watch experts would disagree. The Big Three or the Holy Trinity should be Patek Philippe, founded in 1839; Vacheron Constantin, founded in 1755 and Audemars Piguet, founded in 1875. They are at the forefront of watchmaking, innovation, and luxury since

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Reference: 1. molnupiravir US EUA Product Insert.

MOLNUPIRAVIR Selected Safety Information

Authorized Use

1. Molnupiravir is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults:
   - with positive results of direct SARS-CoV-2 viral testing, and
   - who are at high risk for progression to severe COVID-19, including hospitalization or death, and
   - for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate
2. Molnupiravir is not approved for any use, including the treatment of COVID-19, but is authorized for emergency use by the FDA under an Emergency Use Authorization (EUA).
3. The emergency use of molnupiravir is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1) unless the declaration is terminated or authorization revoked sooner.

Limitations of Authorized Use

4. Molnupiravir is not authorized:
   - for use in patients who are less than 18 years of age
   - for initiation of treatment in patients hospitalized due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19
   - for use for longer than 5 consecutive days
   - or pre-exposure or post-exposure prophylaxis for prevention of COVID-19
5. Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

Contraindications

6. No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.

Warnings and Precautions

7. There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.
8. Molnupiravir is not recommended for use during pregnancy. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
9. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual.
10. Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently during treatment with molnupiravir and for 4 days after the final dose.
11. Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.
12. Hypersensitivity reactions, including anaphylaxis, have been reported with molnupiravir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue molnupiravir and initiate appropriate medications and/or supportive care.
13. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. The safety and efficacy of molnupiravir have not been established in pediatric patients.

Adverse Reactions

14. The most common adverse reactions occurring in ≥1% of subjects in the molnupiravir treatment group in the Phase 3 double-blind MOVe-OUT study were diarrhea (2% versus placebo at 2%),nausea (1% versus placebo at 1%), and dizziness (1% versus placebo at 1%) all of which were Grade 1 (mild) or Grade 2 (moderate).
    Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) of the subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo.

Drug Interactions

15. No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild to moderate COVID-19, have been conducted.

Breastfeeding

16. There are no data on the presence of molnupiravir or its metabolites in human milk. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production. Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.

Males of Reproductive Potential

17. Nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir. The risk beyond three months after the last dose of molnupiravir is unknown.

Before prescribing, please consult the full prescribing information.

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their founding. It was Gerald Genta who designed the first integrated bracelet luxury sports watches, Audemars Piguet Royal Oak and Patek Philippe Nautilus in 1972 and 1976 respectively (Fig. 2).

(a) Left: **Patek Philippe Nautilus 5740G**, introduced in 2018. It became the most complicated model of the Nautilus collection, yet the dimension is very similar to that of the base model 5711. To me, it is one the most good looking and functional sports watches and always reminds me of the slogan: ***You never actually own a Patek Philippe. You merely look after it for the next generation***. It is also a very comfortable watch to wear.

(b) Middle: **Vacheron Constantin 4500V/110A-B128**, introduced in 2016. It is the third generation of the Overseas line, with an innovative quick-release functionality; the Maltese cross-inspired integrated bracelet can be swapped for either of the two straps provided with the watch within seconds. "***Do better if possible, and that is always possible***" is the vision of the company.

(c) Right: **Audemars Piguet Royal Oak Jumbo Extra-Thin "50th Anniversary" 16202OR.OO.1240OR.0**, introduced in 2022, to celebrate the first luxury sports watch, born in 1972. It looks exactly the same as its predecessor 15202 but with a new self-winding movement and the 50-year oscillating weight. The octagon design is a definite winner and matches the motto of the company: To break the rules, you must first master them.

Nowadays, these models are so iconic that one can recognise them from a distance. They become highly sought after and are difficult to acquire.

Fig. 2: The Holy Trinity Sports Watches (Personal Collection)

MY "DRESS WATCHES"

There is no definition for dress watches, usually they are simple, thin and elegant, to be worn with a suit. My interpretation of dress watches should be like these. (Fig. 3)

(a) Left upper quadrant: **F.P. Journe Chronometre a Resonance**, 4th generation, introduced in 2020, to celebrate the 20th anniversary of the first Resonance. It utilises the natural physical resonance without any mechanical transmission phenomenon, previously known as double balance or pendulum. I have to admit this is definitely one of my favourites.

(b) Left lower quadrant: **A. Lange & Sohne Zeitwerk 140.032**, introduced in 2009, displays the time in hours and minutes digitally, a controversial and polarised design. The unique time bridge is part of the movement that penetrates the dial, framing the displays of hours, minutes and seconds. I cannot remember how many times I watched the disc jumping minute by minute, and it felt like magic.

(c) Right upper quadrant: **Patek Philippe 5270P**, introduced in 2018, belongs to the family of perpetual calendars, which can be traced back since 1941 - from reference 1518, 2499, 3970, 5970 to the current reference 5270 - the entire line encompasses only five references. Reference 5270 was the first model of the line to be fitted with an in-house movement. I do not put it in a winder as setting the time, day, year and moon phase is the best way to communicate with the timepiece.

(d) Right lower quadrant: **A. Lange & Sohne Datograph Up/Down 405.035**, introduced in 2012, thirteen years after the first generation in 1999, a major challenge to the Swiss high-end watch manufacturers due to its technical and aesthetic development, raising the bar for in-house, high-end chronograph movements. I totally agree with what Lange CEO Wilhelm Schmid said, "It's a watch people want to wear upside down." And I am so lucky to have the autograph of the late Walter Lange on the accessories of this watch too.

They represent Haute Horology in the watch industry and give me tremendous joy in owning them.

Fig. 3: My "Dress Watches" (Personal Collection)

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INDICATION

BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Important Safety Information for Blenrep (Belantamab mafodotin)

- The most commonly reported adverse reactions were keratopathy including microcyst-like epithelial changes in corneal epithelium with or without changes in visual acuity, blurred vision, and dry eye.
- Patients should be advised to use caution when driving or operating machinery as Blenrep may affect their vision.
- Patients should have an ophthalmic examination performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on Blenrep treatment
- Physicians should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment

BLENREP
belantamab mafodotin

Made for This Moment

Abbreviated Prescribing Information

NAME OF THE MEDICINAL PRODUCT Blenrep **QUALITATIVE AND QUANTITATIVE COMPOSITION** One vial of powder contains 100 mg of belantamab mafodotin. After reconstitution, the solution contains 50mg belantamab mafodotin per mL. **INDICATIONS** Blenrep is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. **POSOLOGY AND METHOD OF ADMINISTRATION** The recommended dose is 2.5 mg/kg of Blenrep administered as an intravenous infusion once every 3 weeks. It is recommended that treatment should be continued until disease progression or unacceptable toxicity. Method of Administration Blenrep must be reconstituted and diluted by a healthcare professional prior to administration as an intravenous infusion. Blenrep should be infused over a minimum of 30 minutes. Recommended Supportive Care Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on treatment. Physicians should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce corneal symptoms.
Dose Modifications
Dose modifications for corneal adverse reactions

Severity	Eye examination findings	Recommended dose modifications
Mild	*Corneal examination finding(s)* Mild superficial keratopathy *Change in BCVA* Decline from baseline of 1 line on Snellen Visual Acuity	Continue treatment at current dose.
Moderate	*Corneal examination finding(s)* Moderate superficial keratopathy *Change in BCVA* Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Withhold treatment until improvement in examination findings and BCVA to mild severity or better. Consider resuming treatment at a reduced dose of 1.9 mg/kg.
Severe	*Corneal examination finding(s)* Severe superficial keratopathy Corneal epithelial defect *Change in BCVA* Decline from baseline of more than 3 lines	Withhold until improvement in examination findings and BCVA to mild severity or better. For worsening symptoms that are unresponsive to appropriate management, consider discontinuation.

Dose modifications for other adverse reactions

Adverse reaction	Severity	Recommended dose modifications
Thrombocytopenia	Grade 2: 3- Platelet count 25,000 to less than 75,000/microlitres	Consider withholding Blenrep and/or reducing the dose of Blenrep to 1.9 mg/kg.
	Grade 4:Platelet count less than 25,000/microlitres	Withhold Blenrep until platelet count improves to Grade 3 or better. Consider resuming at a reduced dose of 1.9 mg/kg.
Infusion-related reactions	Grade 2 (moderate)	Interrupt infusion and provide supportive treatment. Once symptoms resolve, resume at lower infusion rate by at least 50%.
Other Adverse Reactions	Grade 3 or 4 (severe)	Interrupt infusion and provide supportive treatment. Once symptoms resolve, resume at lower infusion rate reduced by at least 50%. If anaphylactic or life threatening infusion reaction, permanently discontinue the infusion and institute appropriate emergency care.
	Grade 3	Withhold Blenrep until improvement to Grade 1or better. Consider resuming at a reduced dose.
	Grade 4	Consider permanent discontinuation of Blenrep. If continuing treatment, withhold until improvement to Grade 1 or better and resume at reduced dose.

WARNINGS AND PRECAUTIONS Corneal adverse reactions Corneal adverse reactions have been reported with the use of Blenrep. The most commonly reported adverse reactions were keratopathy or microcyst-like epithelial changes in corneal epithelium with or without changes in visual acuity, blurred vision, and dry eye symptoms. Patients with a history of dry eyes were more prone to develop changes in the corneal epithelium. Changes in visual acuity may be associated with difficulty in driving or operating machinery. Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed at baseline, before the subsequent 3 treatment cycles and during treatment as clinically indicated. Patients should be advised to administer apreservative-free artificial tears at least 4 times a day during treatment. Patients should avoid using contact lenses until the end of treatment. Patients experiencing keratopathy with or without changes in visual acuity may require a dose modification or treatment discontinuation based on severity of findings. Cases of corneal ulcer have been reported. These should be managed promptly and as clinically indicated by an eye care professional. Treatment with Blenrep should be interrupted until the corneal ulcer has healed. Thrombocytopenia Thrombocytopenic events were frequently reported. Thrombocytopenia may lead to serious bleeding events, including gastrointestinal and intracranial bleeding. Complete blood counts should be obtained at baseline and monitored during treatment, as clinically indicated. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent monitoring and should be managed with a dose delay or dose reduction. Supportive therapy should be provided according to standard medical practice. Infusion-Related Reactions Most IRRs were Grade 1-2 and resolved within the same day. If a grade 2 or higher infusion- related reaction occurs during administration, reduce the infusion rate or stop the infusion depending on the severity of the symptoms. Institute appropriate medical treatment and restart infusion at a slower rate, if the patient's condition is stable. If Grade 2 or higher IRR occurs, administer premedication for subsequent infusions. **INTERACTIONS** No formal drug interaction studies have been performed with Blenrep. **FERTILITY, PREGNANCY AND LACTATION** The pregnancy status of child-bearing women should be verified prior to initiating therapy with Blenrep. Women of child-bearing potential should use effective contraception during treatment with Blenrep and for 4 months after the last dose. Men with female partners of child-bearing potential should use effective contraception during treatment with Blenrep and for 6 months after the last dose. Pregnancy There are no data from the use of Blenrep in pregnant women. Blenrep should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the foetus. Breast-feeding It is not known whether Blenrep is excreted into human milk. Women should be advised to discontinue breast-feeding prior to initiating treatment with Blenrep and for 3 months after the last dose. Fertility Based on findings in animals and the mechanism of action, Blenrep may impair fertility in females and males of reproductive potential. **ADVERSE REACTIONS** The frequency of adverse reactions is defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥ 1/1000 to <1/100). Infections & infestations: Very common: Pneumonia; Common: Upper respiratory tract infection Blood and lymphatic system disorders: Very common: Thrombocytopenia, anaemia, lymphopenia, leukopenia, neutropenia Eye disorders: Very common: Keratopathy, blurred vision events, dry eye events; Common: Photophobia, eye irritation; Uncommon: ulcerative keratitis, infective keratitis Gastrointestinal disorders: Very common: Nausea, diarrhea; Common: Vomiting General disorders and administration site conditions: Very common: Pyrexia, fatigue Investigations: Very common: Increased aspartate aminotransferase, increased gamma glutamyltransferase; Common: Increased creatine phosphokinase Injury, poisoning and procedural complications: Very common: Infusion-related reactions **OVERDOSE** There is no known specific antidote for Blenrep overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate supportive treatment should be instituted immediately.

Abbreviated Prescribing Information based on Blenrep Prescribing Information (HK082021(GDS02/EMA20210729)).

Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong or Level 20, AIA Tower, Nos. 251A - 301 Avenida Comercial De Macau, Macau

For adverse events reporting, please call GlaxoSmithKline Limited at (852) 3189 8989 (Hong Kong) or (853) 2871 5569 (Macau) or email to HK Adverse Event mailbox: HKAdverseEvent@gsk.com

Reference: 1. BLENREP (belantamab mafodotin) Summary of Product Characteristics.

GlaxoSmithKline Limited
23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong
Tel: (852) 3189 8989 Fax: (852) 3189 8931

PM-HK-BLM-ADVT-210001 (09/2023)
Date of preparation : 04/10/2021

THE INDEPENDENTS

Never before in the history of watchmaking have the independent watchmakers been so popular and influential. Their rise in recent years is directly related to the success of F.P. Journe and Philippe Dufour.

Like many talented watchmakers, François-Paul Journe started by restoring vintage clocks and then watches. Upon graduation in 1976, he was exposed to the works of Berthoud and Breguet, whose inventions included tourbillon, natural escapement and resonance. In 1989, Journe, together with Vianney Halter and Denis Flageollet, formed the THA (Techniques Horlogeres Appliquees), which created complications for brands like Audemars Piguet and Cartier. Journe began his own brand in 1999 with a set of Subscription Tourbillons, and the rest is history. He is acclaimed by the Grand Prix d'Horlogerie of Geneva (GPHG) for his horological creations of exception. It makes him the most awarded contemporary watchmaker of his generation. Since 2002, François-Paul Journe has received distinctions every year at the GPHG, except in 2007 and 2009 when he was a member of the Jury, (Fig. 4)

(a) Left: **F.P. Journe, Chronometre Bleu**, introduced in 2009. The simplistic "chrome blue" dial, the Journe's signature hour and minute hands, white printed Arabic numerals, and a small seconds counter between 7 and 8 o'clock makes this watch just perfect in every angle. It is my first Journe watch from the boutique and a very important one!

(b) Middle: **Kurono Tokyo Anniversary 2022 Grand Mori**
The Japanese Hajime Asaoka started by creating custom timepieces. In 2019, he founded Kurono Tokyo to offer affordable watches; the Mori features the traditional Kyoto-style lacquer 'urushi' craftsmanship. Inspired by the canopies of the forest, this pattern on the dial mimics the unveiling of the sun rays seeping through the layers of the trees. There are no boutiques and every enthusiast has to try their luck at a specific time (usually HK time at 22:00) on the day of the global launch. You only have a few minutes.

(c) Right: **Laurent Ferrier Classic Origin LCF036**.T1.G1G, introduced in 2020, in a classic case with a smooth curving line to commemorate the 10th anniversary of the company. I am attracted by the fine finishing and futuristic case design.

Apart from being a technical director at the Patek Phillippe for 37 years, Laurent Ferrier was also a semi-professional car racer, finished third at the Le Mans in 1979, behind Paul Newman.

At the time of writing, I am waiting for the delivery of watches from Laurent Ferrier, the Gronefeld brothers, Kari Voutilainen and my favourite watchmaker F.P. Journe.

Fig. 4: The Independents (Personal Collection)

Going back to the title: Which type of watch collector am I? I do not have an answer as my taste changes along my journey. I only know that I meet a lot of new friends and I am learning something new and exciting every day. These timepieces are a great source of joy for me and I hope you find the same happiness as I do through watch collecting.

Looking forward to meeting and seeing your collections.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				★Zoom HKMA-HKSTP CME Lecture - AI-empowered local bone quality assessment system for osteoporotic bone fracture risk evaluation and surgical planning (Online) **1**	★Zoom Lipid Management for High CV Patients - Online **2**	**3**
4	**5**	★In-person / Zoom HKMA-HKSH CME Programme 2022-2023 (Physical Lecture + Online) ★Certificate Course on Mental Health 2022 (Video Lectures) **6**	★Zoom Common Surgical Conditions - Updates and Recent Advances - Online **7**	★Zoom Practical Tips for Management in the Era of Disease - Specific Migraine Preventives - Online **8**	★Zoom Antiplatelet Management for Post PCI Patients - Online **9**	**10**
11	**12**	★Zoom Counselling Aid: Diagnosis and Treatment Options for Heavy Menstrual Bleeding - Online ★Certificate Course on Mental Health 2022 (Video Lectures) **13**	★The Hong Kong Neurosurgical Society Monthly Academic Meeting - white matter tracts in the era of precision neurosurgery **14**	★Zoom Advances in Chronic Kidney Disease Management - Online ★FMSHK Executive Committee Meeting **15**	**16**	**17**
18	**19**	★Certificate Course on Mental Health 2022 (Video Lectures) **20**	**21**	★Zoom Updates on LDL-C Management: Applying New Guidelines to Clinical Practice - Online **22**	**23**	**24**
25	**26**	**27**	**28**	**29**	**30**	**31**

Date / Time	Function	Enquiry / Remarks
1 THU 2:00 PM	**Zoom** **HKMA-HKSTP CME Lecture - AI-empowered local bone quality assessment system for osteoporotic bone fracture risk evaluation and surgical planning (Online)** Organiser: The Hong Kong Medical Association and Hong Kong Science Park Speaker: Prof William Weijia LU	Mr. Jeff CHENG Tel: 2527 8452 1 CME Point
2 FRI 2:00 PM	**Zoom** **Lipid Management for High CV Patients - Online** Organiser: HKMA-Shatin Community Network Speaker: Dr TSUI Ping-tim	Ms. Candice TONG Tel: 3108 2513 1 CME Point
6 TUE 2:00 PM	**In-person / Zoom** **HKMA-HKSH CME Programme 2022-2023 (Physical Lecture + Online)** **Topic: Interventional Treatment For Metabolic Syndrome** Organiser: The Hong Kong Medical Association and Hong Kong Sanatorium & Hospital Speaker: Dr Daniel King-hung TONG Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Mental Health 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Elvis WH LAI	Ms Vienna LAM Tel: 2527 8898
7 WED 2:00 PM	**Zoom** **Common Surgical Conditions - Updates and Recent Advances - Online** Organiser: HKMA-Central, Western & Southern Community Network Speaker: Dr Cyrus Tak-yin TSE	Ms. Candice TONG Tel: 3108 2513 1 CME Point
8 THU 2:00 PM	**Zoom** **Practical Tips for Management in the Era of Disease - Specific Migraine Preventives - Online** Organiser: HKMA-KLN East Community Network Speaker: Dr LEE Chi-nam	Ms. Candice TONG Tel: 3108 2513 1 CME Point
9 FRI 2:00 PM	**Zoom** **Antiplatelet Management for Post PCI Patients - Online** Organiser: HKMA-KLN City Community Network Speaker: Dr Andrew Kei-yan NG	Ms. Candice TONG Tel: 3108 2513 1 CME Point
13 TUE 2:00 PM	**Zoom** **Counselling Aid: Diagnosis and Treatment Options for Heavy Menstrual Bleeding - Online** Organiser: HKMA-KLN West Community Network Speaker: Dr Queenie Ho-yan WONG	Ms. Candice TONG Tel: 3108 2513 1 CME Point
7:00 PM	**Certificate Course on Mental Health 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHONG King-yee	Ms Vienna LAM Tel: 2527 8898
14 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting - white matter tracts in the era of precision neurosurgery** Organiser: Hong Kong Neurosurgical Society Speaker: Dr LAM Shek-ching Chairman: Dr POON Tak-lap Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	1.5 points College of Surgeons of Hong Kong Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
15 THU 2:00 PM	**Zoom** **Advances in Chronic Kidney Disease Management – Online** Organiser: HKMA-New Territories West Community Network Speaker: Dr AU YEUNG Yick-cheung	Ms. Candice TONG Tel: 3108 2513 1 CME Point
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
20 TUE 7:00 PM	**Certificate Course on Mental Health 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr John SO	Ms Vienna LAM Tel: 2527 8898
22 THU 2:00 PM	**Zoom** **Updates on LDL-C Management: Applying New Guidelines to Clinical Practice - Online** Organiser: HKMA-HK East Community Network Speaker: Dr. Duncan Hung-kwong HO	Ms. Candice TONG Tel: 3108 2513 1 CME Point

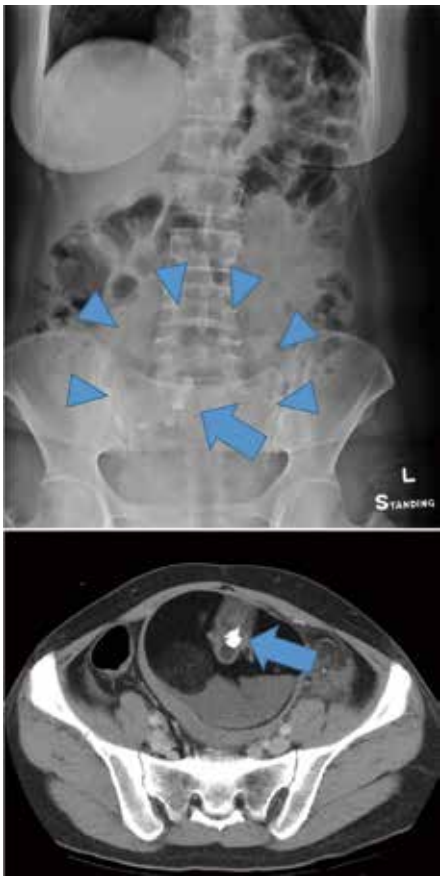
Answers to Radiology Quiz

Answers:

1. A low-density pelvic lesion with a few tooth-like opacities is seen within. There was no dilated bowel, other radiopaque stone, nor pneumoperitoneum.

2. The radiographic features are most compatible with a mature ovarian teratoma (dermoid cyst). Related acute complications of dermoid cysts would be the top differential diagnoses in this clinical context, most commonly ovarian torsion. Other GI causes such as diverticulitis and appendicitis should also be considered.

3. Ultrasound pelvis or CT abdomen and pelvis. Imaging features of mature ovarian teratoma include tissues from different germ cell layers such as fat-fluid levels, teeth, tuft of hair, etc. Common radiological features of ovarian torsion include an enlarged ovary with peripherally displaced follicles, twisted vascular pedicle, and pelvic free fluid.



Dr John Yuen-hei MAK
MBBS, FRCR

WE FORM THE

Backbone of Regimens in **Multiple Myeloma**[1,2]

Revlimid® (lenalidomide)

Pomalyst® (pomalidomide)

Recommended by **NCCN & EHA-ESMO Guidelines** as preferred regimens[1,2]

REVLIMID© is indicated:

- As monotherapy for the maintenance treatment of adult patients newly diagnosed MM who have undergone autologous stem cell transplantation.
- As combination therapy for the treatment of adult patients with previously untreated MM who are not eligible for transplant.
- In combination with DEX for the treatment of MM in adult patients who have received at least one prior therapy.

POMALYST© is indicated:

- In combination with BORT and DEX for the treatment of adult patients with MM who have received at least one prior treatment regimen including REVLIMID©.
- In combination with DEX for the treatment of adult patients with RRMM who have received at least two prior treatment regimens, including both REVLIMID© and BORT, and have demonstrated disease progression on the last therapy.

BORT: bortezomib. DEX: dexamethasone. EHA: European Hematology Association. ESMO: European Society for Medical Oncology. MM: multiple myeloma. NCCN: National Comprehensive Cancer Network. RRMM: relapsed and refractory multiple myeloma.

References:

1. National Comprehensive Cancer Network. NCCN Guidelines: Multiple Myeloma, Version 7.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (accessed on 6 May 2021).
2. Dimopoulos MA, et al. Ann Oncol. 2021;32:309-322.

Abbreviated Prescribing Information: Revlimid® 5 mg, 10 mg, 15 mg, 25 mg hard capsules.
Refer to the full Prescribing Information (PI) before prescribing. Full PI is available on request.
Name of medicine: Revlimid® 5 mg, 10 mg, 15 mg, 25 mg hard capsules. Active ingredient: Lenalidomide. Available dosage forms: Hard capsules containing lenalidomide 5 mg, 10 mg, 15 mg or 25 mg. Indications: Revlimid® as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Revlimid® as combination therapy is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Revlimid® in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Posology and method of administration: For all indications described below: Dose is modified based upon clinical and laboratory findings. Dose adjustments, during treatment and restart of treatment, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide. In case of neutropenia, the use of growth factors in patient management should be considered. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. Newly diagnosed multiple myeloma (Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)): Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L. The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated. Newly diagnosed multiple myeloma (Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant): Lenalidomide treatment must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L. The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. For hematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥ 1.5 x 10^9/L with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle). Newly diagnosed multiple myeloma (Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance in patients who are not eligible for transplant): Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L. The recommended starting dose is lenalidomide 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide monotherapy as follows:10 mg orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression. Multiple myeloma with at least one prior therapy: Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L. The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1 to 4 every 28 days. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient. All indications: For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and then restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion. Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions. Special populations (refer to section 4.2 of the PI for full details): Paediatric population, elderly, patients with renal impairment, patients with hepatic impairment. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Women who are pregnant. Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme (PPP) are met. Warnings (refer to section 4.4 of the PI for full details): Pregnancy warning: If lenalidomide is taken during pregnancy, a teratogenic effect in humans is expected. The conditions of the PPP must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential. Counselling: For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met: She understands the expected teratogenic risk to the unborn child and the need for effective contraception without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment. She should be capable of complying with effective contraceptive measures and understand the need to rapidly consult if there is a risk of pregnancy. Male patients must understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential and understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for at least 4 weeks after dose interruptions and/or cessation of treatment. Contraception: Women of childbearing potential must use at least one effective method of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide in combination therapy, and to a lesser extent in patients with multiple myeloma taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended. Refer to section 4.4 of the PI for full details. Pregnancy testing: According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential. Additional precautions: Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment. Patients should not donate blood during therapy or for at least 4 weeks following discontinuation of lenalidomide. Other special warnings and precautions (refer to section 4.4 of the PI for full details): Myocardial infarction, venous and arterial thromboembolic events, pulmonary hypertension, neutropenia and thrombocytopenia, thyroid disorders, peripheral neuropathy, tumour flare reaction and tumour lysis syndrome, allergic reactions and severe skin reactions (SJS, TEN and DRESS have been reported), lactose intolerance, second primary malignancies, hepatic disorders, infection with or without neutropenia, viral reactivation, progressive multifocal leukoencephalopathy, cataract. Clinically significant interactions: Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. Refer to section 4.5 of the PI for full details. Reported side effects: Very common side effects include a fall in the number of red blood cells which may cause anemia leading to tiredness and weaknesss, rashes, itching, muscle cramps, muscle weakness, muscle pain, muscle aches, bone pain, joint pain, back pain, pain in the extremities, generalised swelling including swelling of your arms and legs, weakness, tiredness, fever and flu like symptoms including fever, muscle ache, headache, earache, cough and chills, numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, tremor, decreased appetitie, changes in the way things taste, increase in pain, tumour size or redness around the tumour, weight loss, constipation, diarrhoea, nausea, vomiting, stomach pain, heartburn, low levels of potassium or calcium and/or sodium in the blood, thyroid disorders less than it should be, leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs, called pulmonary embolism), infections of all types, including infection of the sinuses that surround the nose, infection of the lung and the upper respiratory tract, shortness of breath, blurred vision, clouding of your eye (cataract), kidney problems which include kidneys not working properly or not being able to maintain normal function, abnormal liver test results, increase in liver test results, changes to a protein in the blood that can cause swelling of the arteries (vasculitis), increases in your blood sugar levels (diabetes), decreases in your blood sugar levels, headache, nosebleed, dry skin, depression, mood change, difficulty sleeping, cough, a fall in blood pressure, a vague feeling of bodily discomfort, feeling bad, sore inflamed mouth, dry mouth, dehydration. Please refer to section 4.8 of the PI for other side effects seen on treatment with lenalidomide. Date of revision of prescribing information: 14 May 2021.

Abbreviated Prescribing Information: Pomalyst® 1 mg, 2 mg, 3 mg, 4 mg hard capsules.
Refer to the full Prescribing Information (PI) before prescribing. Full PI is available on request.
Name of medicine: Pomalyst® 1 mg, 2 mg, 3 mg, 4 mg hard capsules. Active ingredient: Pomalidomide. Available dosage form: Hard capsules containing pomalidomide 1 mg, 2 mg, 3 mg or 4 mg. Authorised indications: Pomalyst® in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide. Pomalyst® in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. Posology and method of administration: Dosing is continued or modified based upon clinical and laboratory findings. Pomalidomide in combination with bortezomib and dexamethasone: The recommended starting dose of Pomalyst® is 4 mg orally once daily on Days 1 to 14 of repeated 21-day cycles. Pomalidomide is administered in combination with bortezomib and dexamethasone, as shown in Table 1 of the full PI. Please refer to section 4.2 of the PI for the recommended dosing scheme for Pomalyst® in combination with bortezomib and dexamethasone. Pomalidomide in combination with dexamethasone: The recommended starting dose of Pomalyst® is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle. Treatment with pomalidomide combined with dexamethasone should be given until disease progression or until unacceptable toxicity occurs. Pomalidomide must be discontinued for exfoliative or bullous rash, or if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions. Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued permanently for angioedema and anaphylactic reaction. Special populations: Elderly: Please refer to section 4.2 of the full PI for details. Paediatric population. There is no relevant use of pomalidomide in children aged 0-17 years for the indication of multiple myeloma. Renal impairment. No dose adjustment of pomalidomide is required for patients with renal impairment. On haemodialysis days, patients should take their pomalidomide dose following haemodialysis. Hepatic impairment. Patients with serum total bilirubin >1.5 x ULN (upper limit of normal range) were excluded from clinical studies. Hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide. No adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed. Contraindications: Pregnancy. Women of childbearing potential, unless all the conditions of the pregnancy prevention programme are met. Male patients unable to follow or comply with the required contraceptive measures. Hypersensitivity to the active substance or to any of the excipients. Warnings: Pregnancy warning. Pomalidomide must not be taken during pregnancy, since a teratogenic effect is expected. The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential. Refer to Section 4.4 of the PI for a full list of the criteria for women of non-childbearing potential. Breast-feeding. It is not known if pomalidomide is excreted in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother. Counselling. For women of childbearing potential, pomalidomide is contraindicated unless all of the following are met: She understands the expected teratogenic risk to the unborn child. She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment. She should be capable of complying with effective contraceptive measures, and understands the need to undergo medically supervised pregnancy tests. For male patients taking pomalidomide, he understands the expected teratogenic risk if engaged in sexual activity with a woman of childbearing potential and he understands the need for the use of a condom during treatment duration, during dose interruption and for 4 weeks after dose interruptions and/ or cessation of treatment. Contraception. Women of childbearing potential must use at least one effective method of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after pomalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. Please refer to section 4.4 of the PI for examples of suitable methods of contraception. Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed in Section 4.4 of the PI. Pregnancy testing. According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential. Please refer to Section 4.4 of the PI for full details of pregnancy testing. Additional precautions. Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment. Patients should not donate blood, semen or sperm during treatment (including during dose interruptions) and for 4 weeks following discontinuation of pomalidomide. Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule. Other special warnings and precautions (refer to section 4.4 of the PI for full details): Haematological events, thromboembolic events, thyroid disorders, peripheral neuropathy, significant cardiac dysfunction, tumour lysis syndrome, second primary malignancies, allergic reactions and severe skin reactions, dizziness and confusion, interstitial lung disease, hepatic disorders, infections, progressive multifocal leukoencephalopathy. Clinically significant interactions: Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug interactions due to P450 isoenzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters. Refer to section 4.5 of the PI for full details. Reported side effects: Anaemia, neutropenia, thrombocytopenia, fatigue, pyrexia, oedema peripheral, pneumonia, peripheral sensory neuropathy. Prescribers should consult the full Prescribing Information in relation to other side-effects. Date of revision of abbreviated prescribing information: 18/12/2020.

Bristol Myers Squibb™

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2204-HK-2200007 Oct 2022

Hope of life beyond CD30+ lymphoma[1]*

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ONCOLOGY

Abbreviated Prescribing Information (EU-DEC20-HK-MAR21)
ADCETRIS 50 mg powder for concentrate for solution for infusion.
Active Ingredient: Brentuximab vedotin Indication: Treatment for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD); Treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; Treatment for relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; In combination with cyclophosphamide, doxorubicin and prednisone (CHP) for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL); relapsed or refractory sALCL; Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy. Dose & Administration: Previously untreated HL: In combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] (AVD)), 1.2mg/kg IV infusion over 30 min on days 1 and 15 of each 28-day cycle for 6 cycles. HL at increased risk of relapse or progression following ASCT & CTCL after at least 1 prior systemic therapy: 1.8 mg/kg IV infusion over 30 min every 3 wk up to max of 16 cycles. Previously untreated sALCL: In combination with chemotherapy (cyclophosphamide [C], doxorubicin [H] and prednisone [P] (CHP)), 1.8 mg/kg IV infusion over 30 minutes every 3 weeks for 6 to 8 cycles. Relapsed or refractory HL & relapsed or refractory sALCL: 1.8 mg/kg IV infusion over 30 min every 3 wk, patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a max of 16 cycles. Contraindications: Hypersensitivity to brentuximab. Combined use of brentuximab & bleomycin. Pregnancy & lactation. Special Population: Closely monitor for new or worsening neurological, cognitive or behavioural signs or symptoms suggestive of progressive multifocal leukoencephalopathy (PML); new or worsening abdominal pain suggestive of acute pancreatitis; new or worsening pulmonary symptoms; emergence of serious & opportunistic infections; immediate & delayed infusion-related reactions. Discontinue use if anaphylaxis & Stevens-Johnson syndrome occurs. Patient w/rapidly proliferating tumour & high tumour burden at risk of tumour lysis syndrome. Monitor for symptoms of neuropathy. Patient experiencing new or worsening peripheral neuropathy may require delay & dose reduction or discontinuation of treatment. Monitor CBC prior to therapy; serum glucose. Patient w/ an elevated BMI w/ or w/o history of DM; renal & hepatic impairment; on controlled Na-diet. Women of childbearing potential should use 2 methods of contraception during & until 30 days after therapy. Men should not father a child during therapy & for up to 6 mth after last dose. May affect ability to drive or operate machinery. Childn & elderly. Adverse Reactions: Infection, sepsis/septic shock, upper resp tract infection, herpes zoster, pneumonia, neutropenia, anaemia, thrombocytopenia, hyperglycaemia, peripheral sensory neuropathy, peripheral motor neuropathy, dizziness, demyelinating polyneuropathy, cough, dyspnoea, diarrhoea, nausea, vomiting, constipation, elevation of ALT/AST, alopecia, pruritus, rash, myalgia, arthralgia, back pain, fatigue, pyrexia, infusion-related reactions & chills.

For detailed information, please consult full prescribing information.
For reporting suspected side effects for Takeda products at AE.HongKong@takeda.com
For asking medical information and other inquiries for Takeda products at medinfohk@takeda.com

Reference: 1* Adcetris Package Insert, EU-DEC20-HK-MAR21

C-APROM/HK/ ADCE/0031103/2022