Application Number 1420 to the
Medical Services Advisory Committee

For the listing of integrated, closed-system ECP systems

For the treatment of acute and chronic graft-versus-host disease

PROTOCOL
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Mallinckrodt
166 Epping Rd, Lane Cove West, NSW, 2066

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ABBREVIATIONS AND TERMS

aGVHD	acute graft-versus-host disease
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australian Refined Diagnostic Related Group
ARTG	Australian Register of Therapeutic Goods
BSA	body surface area
CC	complication and/or comorbidity
CCC	catastrophic Complication and/or comorbidity
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CSCC	catastrophic or Severe Complication and/or comorbidity
DAP	Decision Analytic Protocol
DPMQ	dispensed price for max quantity
DRG	Diagnostic Related Group
ECP	extracorporeal photopheresis
GVHD	graft-versus-host disease
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
ICER	incremental cost-effectiveness ratio
ITT	intent-to-treat
KOL	key opinion leader
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
mTOR	mammalian target of rapamycin
NA	not applicable
NR	not reported
PASC	Protocol Advisory Sub Committee
PBAC	Pharmaceutical Benefit Advisory Committee
PBS	Pharmaceutical Benefits Scheme
QoL	Quality of life
TGA	Therapeutic Goods Administration
TNF	tumour necrosis factor
UVA	ultraviolet A

1 TITLE OF APPLICATION

The use of integrated, closed-system Extracorporeal Photopheresis (ECP) with ultraviolet-A (UVA) irradiation in conjunction with a photoactive drug methoxsalen for the treatment of acute and chronic graft-versus-host disease after haematopoietic stem cell transplantation.

2 PURPOSE OF APPLICATION

Please indicate the rationale for the application and provide one abstract or systematic review that will provide background

Extracorporeal Photopheresis (ECP) is a leukapheresis-based, autologous immunomodulatory therapy where white blood cells are separated from whole blood via apheresis, combined with a photoactive drug, methoxalen (UVADEX®), and then exposed to ultra violet A (UVA) light. All blood components, including the treated white blood cells are returned to the patient. The integrated, closed-system ECP system comprises a closed photopheresis technology, which greatly improves the safety and efficiency of this service compared with the open system.

Graft-versus-host disease (GVHD) is an immune-mediated disease which remains a major complication following allogeneic hematopoietic stem cell or bone marrow transplant. Despite prophylactic immunosuppression, hematopoietic stem cell transplantation (HSCT) is currently associated with a 50% risk of GVHD overall [1, 2] which may contribute to 17-20% of transplant-related deaths regardless of donor-relatedness [3]. According to the National Institutes of Health (NIH) consensus criteria [4], GVHD can be classified into acute GVHD (aGVHD) and chronic GVHD (cGVHD) based on clinical manifestations. aGVHD typically includes a classic maculopapular rash, persistent nausea, abdominal cramps with diarrhoea, and rising serum bilirubin. cGVHD commonly shows skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma, dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract, liver abnormalities, and a higher serum bilirubin level.

The mainstay of treatment for GVHD is systemic steroid therapy [5]. Corticosteroids such as prednisone and methylprednisolone are first-line therapy for aGVHD, but are associated with low rates of durable complete response (24%–44%) [6-8] and approximately 60% of patients with cGVHD achieve inadequate response to first-line steroids [9]. The most effective approach to steroid-refractory/intolerant/dependent GVHD remains controversial. Based on recent evidence demonstrating significant improvements in GVHD and survival benefits, ECP is recommended by international guidelines and consensus documents as a second-line treatment for steroid-refractory, steroid-intolerant or steroid-dependent acute and chronic GVHD [10-12].

In Australia, integrated, closed-system ECP is currently registered with the Therapeutic Goods Administration (TGA) for the administration of photopheresis. It is established in Australian clinical practice in the management of acute and chronic GVHD; however, the integrated, closed-system ECP service, including the procedures, therapies and consumables, is not publicly subsidised via reimbursement pathways such as Medicare Benefit Schedule (MBS) or Pharmaceutical Benefits Scheme (PBS). Currently, the integrated, closed-system ECP service provided in Sydney and Melbourne is partially reimbursed via ad-hoc state funding arrangements, which limits treatment to a select few.

This protocol is seeking MBS listing of the integrated, closed-system ECP service to be used in conjunction with the active ingredient methoxsalen, for the treatment of steroid-refractory, steroid-intolerant or steroid-dependent acute and chronic GVHD via a co-dependent MSAC/PBAC application.

Please refer the abstract in Appendix 1 for further background on ECP in the treatment for acute and chronic GVHD: *Abu-Dalle, I; Reljic, T; Nishihori, T, et al. (2014). "Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies." Biol Blood Marrow Transplant 20(11): 1677-1686.*

3 POPULATION AND MEDICAL CONDITION

3.1 DESCRIPTION OF MEDICAL CONDITION

GVHD is a common, serious and sometimes fatal immune-mediated disease resulting from a complex interaction between donor and recipient adaptive immunity [13, 14]. Activated donor T cells attack the tissues of the transplant recipient as antigenic differences cause the immune response to recognise host tissues as antigenically foreign. The resulting inflammatory cytokines cause tissue damage, with the most commonly involved organs including the liver, skin, mucosa, and the gastrointestinal tract.

Classically, GVHD appearing within 100 days post transplant was considered acute GVHD (aGVHD), whereas GVHD appearing after day 100 was described as chronic GVHD (cGVHD). However, aGVHD may occur later than 100 days post transplant and some patients may develop an overlap syndrome, where features of both acute and chronic GVHD are present [8, 15]. According to the National Institutes of Health (NIH) consensus criteria [4], GVHD can be classified into aGVHD and cGVHD based on clinical manifestations:

- Acute GVHD typically includes a classic maculopapular rash, persistent nausea and/or emesis, abdominal cramps with diarrhoea, and a rising serum bilirubin concentration.

- Patients with cGVHD commonly demonstrate skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma, dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract, liver abnormalities, and a rising serum bilirubin concentration.

The severity of aGVHD is categorised as grade I-IV based on modified Glucksberg criteria [16]. These grading criteria (first published by Glucksberg et al in 1974) are based on the number of organs involved and the degree to which they are affected (Table 1).

Table 1: aGVHD grading based on modified Glucksberg criteria

Stage	Cutaneous rash	Hepatic *(bilirubin)*	Gut *(diarrhoea/nausea)*
1	<25% BSA	34-50 mmol/L	>500mL or nausea
2	35-50% BSA	51-102 mmol/L	> 1000mL
3	Generalised erythroderma	103-255 mmol/L	>1500mL
4	Generalised erythroderma with bullae and desquamation	>255 mmol/L	Pain/Ileus
Functional grading	**Cutaneous**	**Hepatic**	**Gut**
I	Stages 1 and 2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III and IV	Stage 4 or	Stages 2-4 or	Stages 2-4

Abbreviations: BSA, body surface area.
Source: [16]

Chronic GVHD can involve any organ and is scored as mild, moderate, severe according to the number of organs involved and the degree to which they are affected [4]. Details are presented in Table 2.

Table 2: NIH global severity of chronic GVHD

Mild chronic GVHD 1 or 2 Organs involved with no more than score 1 *plus* Lung score 0 Moderate chronic GVHD 3 or More organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1 Severe chronic GVHD At least 1 organ with a score of 3 OR Lung score of 2 or 3 Key points: In skin: higher of the 2 scores to be used for calculating global severity. In lung: FEV1 is used instead of clinical score for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Source: [4].

Incidence rates of aGVHD range from 30% to 60% in patients who receive allogeneic HSCT from an HLA-identical sibling, but it is also common in matched-unrelated and haploidentical-related donors [17]. A recent, large study (N=775) reported an aGVHD incidence rate of 44.7% (92% with classic aGVHD vs 8% with late-onset aGVHD) [18]. Based on a retrospective analysis of 5561 adults receiving allogeneic hematopoietic stem cell transplants between 1999 and 2005 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), the cumulative incidence of aGVHD was 39% for HLA-identical sibling donors and 59% for HLA-identical unrelated donors [2].

Acute GVHD is a risk factor for developing cGVHD [19], however cGVHD is not simply an evolution of preceding aGVHD [15]. Lee *et al* (2009) reported chronic GVHD to be a complication of HSCT in 64%-81% of patients [20], whereas Flowers *et al* 2011 reported the incidence of cGVHD to be 34% [15].

3.2 PROPOSED PATIENT POPULATION

The proposed patient populations who would benefit from the use of integrated, closed-system ECP with UVA irradiation in conjunction with a photoactive drug methoxsalen are:

- Adults and paediatrics with grade II-IV aGVHD following HSCT who are steroid-refractory or steroid-dependent or steroid-intolerant [16].
- Adults and paediatrics with cGVHD following HSCT who are steroid-refractory or steroid-dependent or steroid-intolerant [11].

British consensus statement definitions for the steroid-refractory, -dependent and -intolerant aGVHD are as follows [16]:

- Steroid-refractory aGVHD is defined as worsening of aGVHD after 3 days of systemic corticosteroids (minimum dose of 1 mg/kg) or no improvement after 7 days of systemic corticosteroids (minimum dose of 1 mg/kg).

- Steroid-dependent aGVHD is defined as recurrence of aGVHD (grade II or higher) during corticosteroid taper and before reaching 50% of initial starting dose of corticosteroids.

- Steroid-intolerant aGVHD defined as patients with aGVHD who are unable to tolerate the side effects of adequate doses of systemic steroids.

The 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD define cGVHD patients who are steroid-refractory or steroid-dependent as following:

- Steroid-refractory cGVHD may be defined when manifestations progress despite the use of a regimen containing prednisone at >1 mg/kg/day for at least 1 week or persist without improvement despite continued treatment with prednisone at >.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks [21].

- Steroid-dependent cGVHD may be defined when prednisone doses > 0.25 mg/kg/day or > 0.5 mg/kg every other day are needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least 2 occasions, separated by at least 8 weeks. These suggested dose thresholds match the average doses from 3 months onward in a prospective study of first-line treatment [21].

Steroid-intolerant cGVHD defined as patients with cGVHD who are unable to tolerate the side effects of adequate doses of systemic steroids (KOL opinion).

3.3 EVIDENCE FOR PROPOSED PATIENT POPULATION

Clinical evidence identified to support the proposed patient population in both acute and chronic GVHD is listed below. All individual trials and those included in systematic reviews enrolled acute or chronic GVHD patients who were refractory to, or intolerant to, or dependent on the initial steroids therapy. The body of evidence also formed the basis for a series of treatment guidelines and consensus statements for acute and chronic GVHD [11, 16, 22, 23]. Consultation with key opinion leaders (KOL) in the management of GVHD in Australia, has verified that the proposed patient population is consistent with current integrated, closed-system ECP practice in the Australian context.

- Acute GVHD
    - Zhang et al (2015)[24]: a systematic review of ECP in seven prospective studies with a total of 121 steroid-refractory aGVHD patients. The overall response rate (ORR) was 0.71 and the complete response rate (CRR) was 0.71. The efficacy of ECP for skin aGVHD, liver aGVHD, and gut aGVHD were 0.86, 0.60, and 0.68, respectively. ECP is an effective therapy for skin, liver, and gut aGVHD.
    - Abu-Dalle et al (2014) [25]: a systematic review of prospective studies of ECP in patients with acute and chronic steroid-refractory or steroid-dependent GVHD. Nine studies of 323 patients were included in the meta-analysis. In acute GVHD, the pooled overall response rate (ORR) was 0.69 (95% CI: 0.34 to 0.95). In terms of organ-specific responses, ECP resulted in the highest ORR for cutaneous, with 0.84 (95% CI: 0.75 to

0.92), followed by gastrointestinal with 0.65 (95% CI: 0.52 to 0.78). ECP-related mortality rates were extremely low. Rates of immunosuppression discontinuation were 0.55 (95% CI: 0.40 to 0.70).

- Jagasia et al (2013) [26]: a large, multicentre, retrospective comparison of ECP (86 patients) and anticytokine therapy (inolimomab or anti-TNF-α, 41 patients) for second-line treatment of adult patients with steroid-dependent and -refractory aGVHD. The aGVHD response was higher in the ECP group (73% vs 32%; P<0.001) and was associated with a superior survival (not reached vs 4.9 months; P<0.001). The cumulative incidence of 2-year non-relapse mortality was higher in the non-ECP group compared with the ECP group (82% vs 37%; P<0.001). This study suggests that ECP is an effective second-line therapy for aGVHD and may be superior to non-ECP intervention.
- Dall'Amico (2002) [27]: a retrospective study of ECP in aGVHD. CR in patients with the following organ involvement: Skin, 67%; Liver, 38%; Gut, 54%. Immunosuppressive therapy was discontinued in 28% of cases and reduced in 46%.

- Chronic GVHD
  - Malik et al (2014) [28]: a systematic review of retrospective and prospective studies of ECP in patients with chronic steroid-refractory GVHD. A total of 595 patients across 18 studies were analysed. Pooled CR rates and ORR were 29% (95% CI: 19–42%) and 64% (95%CI, 65– 82%), respectively. One-year overall survival was available for 4 studies only and was 49% (95% CI, 29–70%). The pooled RR for skin, liver, ocular, oral, lung, gastrointestinal and musculoskeletal SR-cGVHD was 74%, 68%, 60%, 72%, 48%, 53%, and 64%, respectively. No significant differences in responses to ECP for paediatric and adult populations were found.
  - Abu-Dalle et al (2014) [25]: a systematic review of prospective studies of ECP in patients with acute and chronic steroid-refractory or steroid-dependent GVHD. Nine studies of 323 patients were included in the meta-analysis. In cGVHD, the pooled overall response rate (ORR) was 0.64 (95% CI: 0.47 to 0.79). Organ-specific response was high in cGVHD involving the skin and gastrointestinal tract, but low in the lung involvement. ECP-related mortality rates were extremely low. Rates of immunosuppression discontinuation were 0.23 (95% CI: 0.07 to 0.44).
  - Flowers et al (2008) [29]: A multicenter prospective phase 2 randomised study compared ECP plus standard therapy with standard therapy alone in ECP in cGVHD. The median percentage improvement in Total Skin Score (TSS) at week 12 was 14.5% for the ECP arm and 8.5% for the control arm (P =0.48). The proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease from baseline in TSS was 8.3% in the ECP arm at week 12 and 0% in the control arm (P <0.04). The nonblinded investigator assessment of skin complete or partial responses revealed a significant improvement in favour of ECP (P <0.001). ECP was generally well tolerated and may have a steroid sparing effect in the treatment of cGVHD.

3.4 EXPECTED UTILISATION

There is a high unmet clinical need for GVHD patients to receive integrated, closed-system ECP as a reimbursed treatment, as it is currently used off label through ad hoc state funding. Integrated, closed-system ECP offers significant clinical benefit over the current standard of care with a preferable safety profile, and has proven to be more effective than many of its competitors within a local context (Appendix 2). Reimbursement of integrated, closed-system ECP will encourage equal access to the service. However the increase in patient population will not be huge as it has already been used in current clinical practice.

An epidemiological approach will be applied to estimate the utilisation of the integrated, closed-system ECP in aGVHD and cGVHD based on current clinical practice and a number of assumptions/estimates of the prevalence and/or incidence of aGVHD and cGVHD, and proportions of patients who are eligible for treatment.

4 INTERVENTION

4.1 DESCRIPTION OF PROPOSED MEDICAL SERVICE

4.1.1 Integrated ECP systems overview

ECP treatment is well established, with a large body of evidence showing treatment effectiveness, including single arm studies [26, 27, 30-33], randomised trials [29, 34], and guidelines and reviews of the treatment [10, 11, 16, 24, 25, 28, 35]. The existing body of evidence forms the basis for the proposed MSAC submission.

ECP systems come in open and closed systems. The open ECP systems are characterised by separate devices for cell separation and drug photo activation, also known as two-step methods [35]. In these systems the combination of the device for separation and the device for photoactivation has not been approved either for use together or specifically approved for photopheresis [35]. The multiple step approach also increases the potential risk of patient re-infusion error, infection and cross-contamination [35, 36]. Open systems are also restricted for use in centres that have approval for handling blood components separately [35].

Integrated, closed-system ECP systems (also known as closed system) complete the processes of cell separation, photo activation of the drug, and reinfusion of the treated cells back into the patient within an automated and fully integrated process [35]. All components of the treatment are validated for use together. The integrated system reduces the risk of infection, contamination and errors during reinfusion compared with open systems [35] .

Integrated, closed-system ECP treatment has established a place within the GVHD treatment supported by a number of published studies, and has been recognised as having the “least side effects” across current available treatments.

In Australia, integrated, closed-system ECP devices are currently registered with the TGA for the following indications:

- Cellex System (kit or system) is indicated for the administration of Photopheresis.

Note: the indication for integrated, closed-system ECP has recently been amended to the above stated indication. However the TGA website is currently displaying the previous indication.

4.1.2 Components of integrated, closed-system ECP system

Integrated, closed-system ECP is an immune-modulatory therapy in which a patient’s leukocytes are collected and treated outside of the body with both methoxsalen and UVA irradiation and then returned into the patient. Integrated, closed-system ECP involves two components, the integrated, closed-system ECP device that incorporates the UVA irradiation system and the photosensitive agent, which is a liquid formulation of the photoactive drug methoxsalen. As there is both a device and a drug used, the submission being prepared for this treatment is a hybrid co-dependent submission.

Anticoagulants, such as a heparinised saline solution, are used as part of ECP treatment in priming the system and throughout patient treatment. Volume replacement fluid and/or volume expanders (such as albumin) are considered optional; however they are another component potentially used during the procedure.

4.1.3 How integrated, closed-system ECP system works

Integrated, closed-system ECP delivers the photo immune-modulatory therapy in which white blood cells are separated from whole blood via apheresis, combined with the photoactive drug methoxsalen (UVADEX®), and exposed to UVA light. All blood components, including the treated white blood cells are returned to the patient (simultaneously in dual needle mode and intermittently in single needle mode).

Integrated, closed-system ECP produces clinical improvements in steroids refractory/resistant/intolerant GVHD. However, immunological mechanisms of ECP are still under investigation. It is known that the combination of 8-MOP and UVA radiation causes apoptosis of treated leukocytes and may cause preferential apoptosis of activated or abnormal T cells [35]. However, given that only a small percentage of the body's lymphocytes are treated, this is not likely the only mechanism of action. It is speculated that once the treated cells are reinfused into the patient, it induces a systemic immunomodulatory response, including an increase in anti-inflammatory cytokines, a decrease in pro-inflammatory cytokines, and an increase in regulatory T cells[37-39]. It is thought that through this process that integrated ECP treatment induces the systemic changes within a GVHD patients' immune system.

It should also be noted that patients receiving integrated, closed-system ECP treatment respond normally to unrelated immune challenges, such as exposure to foreign pathogens[40]. ECP treatment does not appear to change the frequency of viral reactivations either and patients do not develop the infections associated with an immunosuppressant [11, 23, 36, 41].

4.2 TECHNICAL SPECIFICATION

Photopheresis or ECP is a photo immune therapy where white blood cells are separated from whole blood via apheresis, combined with a photoactive drug (8-methoxypsoralen) and then exposed to UVA light. All blood components, including the treated white blood cells are returned to the patient.

THERAKOS® Photopheresis utilises the THERAKOS® CELLEX® Photopheresis System to combine state of-the-art cell separation and photoactivation into a single, closed and sterile circuit. The THERAKOS® CELLEX® Photopheresis System collects the buffy coat (leukocyte-enriched blood) from the patient in a continuous flow process and simultaneously (DOUBLE NEEDLE mode) or intermittently (SINGLE NEEDLE mode) returns the remaining cells to the patient. The buffy coat is passed through the Photoactivation Module where the drug is activated with a precise amount of UVA light determined by the characteristics of the individual patient's buffy coat. After photoactivation, the buffy coat is promptly returned to the patient bloodstream

A full system description can be found in Appendix 3, the CELLEX operator's manual revision 6.0.

4.3 REGISTERED TRADEMARK WITH DISTINGUISHING CHARACTERISTICS

The proposed integrated, closed-system ECP service utilises a specialised device with a registered trademark of THERAKOS™ photopheresis system.

4.4 PROPOSED SETTING FOR DELIVERY

The KOL indicates that in Australia acute GVHD patients are generally treated in the inpatient setting due to the more severe nature of the disease, and chronic GVHD patients are generally treated in the outpatient setting.

It is noted that the integrated, closed-system ECP device is not portable. The proposed service should only be delivered in highly specialised haematology clinical centres where access to the integrated, closed-system ECP is available. Currently, there are two Therakos ECP devices operating in Australia: one in the Peter MacCallum Cancer Centre in Melbourne, and the other in the Royal Prince Alfred Hospital in Sydney The ongoing nature of the integrated, closed-system ECP treatment may require rural and remote patients (and their families) to relocate to a major population centre. Although travelling to treatment centres may be an option for some patients when the integrated, closed-system ECP is required, it is noted that some of the GVHD patients may be seriously ill and unable to travel.

Provision of the integrated, closed-system ECP in very small children is difficult and requires a network of specialised clinical staff that are capable of operating in a specialised environment designed for paediatric patients.

4.5 SERVICE DELIVERY IN CLINICAL SETTING

The integrated, closed-system ECP schedules for acute and chronic GVHD are different. Detailed schedules, which have been confirmed with KOL as being in line with clinical practice in the Australian setting, are detained below:

- aGVHD [16]
    - Treatment initiation: One cycle of treatment (i.e. ECP on two consecutive days) should be initiated weekly for a minimum of eight cycles (8 weeks). Patients with grade III–IV aGVHD may benefit from three treatments per week for the first 4 weeks.
    - Assessment after 8 weeks of ECP therapy:
        - Adult patients who have achieved a complete clinical response and are receiving a steroid dose of <20 mg per day methylprednisolone or 25 mg prednisolone or children on <0.5 mg/kg may be able to stop ECP treatment after 8 weeks of therapy. Otherwise, continue with weekly cycles of ECP with weekly assessments and stop as soon as no further response.
        - Patients who have achieved a partial clinical response at 8 weeks but are still requiring steroid doses of >20 mg per day methylprednisolone or 25 mg per day prednisolone in adults or >0.5 mg/kg in paediatric patients to continue with weekly cycles of ECP with weekly assessments and stop as soon as no further response.
        - A tapering schedule is advised for those with lower GI aGVHD who show a response to ECP, dropping to 2-weekly cycles after 8 weeks and then to monthly cycles according to response before discontinuing therapy.
        - Patients without at least a PR after 8 weeks should be considered for alternative therapy.

- cGVHD [29]
    - 3 times during week 1 and then twice weekly on consecutive days during weeks 2 through 12. Responding patients in the ECP group could continue 2 ECP treatments every 4 weeks until no further response.

5 CO-DEPENDENT INFORMATION

Treatment with integrated, closed-system ECP involves both the ECP device itself and a photoactive drug methoxsalen, which is not indicated for use within GVHD patients. Unlike a typical co-dependant submission, the use of methoxsalen within the integrated, closed-system ECP treatment is not a drug dependant on a diagnostic test. Therefore it should be considered as a hybrid technology, with the device being inseparable from the drug, and vice versa.

The proposed PBS restriction of methoxsalen is outlined as follows:

Section 100 HSD
Authority Required *(private hospitals)*
Authority Required (STREAMLINED) *(public hospitals)*

Note
Treatment centres are required to have access to the specialised haematologists for the provision of clinical consultation services for GVHD

Authority required
Acute graft-versus-host disease
Clinical criteria:
Adult and paediatric patient must have acute graft-versus-host disease following allogeneic HSCT,
AND
Patient must have been refractory to, intolerant to or dependent on steroids,

- Steroid-refractory aGVHD is defined as worsening of aGVHD after 3 days of systemic corticosteroids (minimum dose of 1 mg/kg) or no improvement after 7 days of systemic corticosteroids (minimum dose of 1 mg/kg).

- Steroid-dependent aGVHD is defined as recurrence of aGVHD (grade II or higher) during corticosteroid taper and before reaching 50% of initial starting dose of corticosteroids.

- Steroid-intolerant aGVHD defined as patients with aGVHD who are unable to tolerate the side effects of adequate doses of systemic steroids

AND
Patient must have a grade II-IV acute graft-versus-host disease according to modified Glucksberg criteria.
Patient criteria:
Patients must not be pregnant
Patient must have no idiosyncratic reactions to psoralen compounds
Patient must have no history of light-sensitive disease (such as systemic lupus erythematous, xeroderma pigmentosum, or aphakia)
Patient must have no history of heparin-induced thrombocytopenia
Patient must have no impaired cardio-circulatory function
Treatment criteria:
Must be treated in an accredited treatment centre.
Must be treated with an integrated, closed-system Extracorporeal Photopheresis (ECP) device.

Chronic graft-versus-host disease
Clinical criteria:
Adult and paediatric patient must have chronic graft-versus-host disease following allogenetic HSCT, AND
Patient must have been refractory to, intolerant to or dependent on steroids.

- Steroid-refractory cGVHD may be defined when manifestations progress despite the use of a regimen containing prednisone at >1 mg/kg/day for at least 1 week or persist without improvement despite continued treatment with prednisone at >.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks

- Steroid-dependent cGVHD may be defined when prednisone doses > 0.25 mg/kg/day or > 0.5 mg/kg every other day are needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least 2 occasions, separated by at least 8 weeks. These suggested dose thresholds match the average doses from 3 months onward in a prospective study of first-line treatment

- Steroid-intolerant cGVHD defined as patients with cGVHD who are unable to tolerate the side effects of adequate doses of systemic steroids

Patient criteria:
Patients must not be pregnant
Patient must have no idiosyncratic reactions to psoralen compounds
Patient must have no history of light-sensitive disease (such as systemic lupus erythematous, xeroderma pigmentosum, or aphakia)Patient must have no history of heparin-induced thrombocytopenia
Patient must have no impaired cardio-circulatory function
Treatment criteria:
Must be treated in an accredited treatment centre.
Must be treated with an integrated, closed-system Extracorporeal Photopheresis (ECP) device.

6 COMPARATOR AND CLINICAL CLAIM

6.1 COMPARATOR

The comparator for the proposed medical service is likely to be a basket of second-line treatment options of immunosuppressive and immunomodulatory agents that form best supportive care, as recommended in the BCSH/BSBMT guidelines [10] for aGVHD and the European/BCSH/BSBMT guidelines [11, 12] for cGVHD, respectively. However, in many cases ECP is unlikely to initially replace immunosuppressive and immunomodulatory agents and may be used to avoid higher doses (and side effects) and withdraw patients from these therapies. The KOL concurred with the comparators nominated in this application. As integrated, closed-system ECP is currently an option of the second-line treatment (limited to two hospitals in Australia), determining an appropriate comparator is complex and is likely influenced by location and other clinical characteristics.

None of the nominated second-line treatments are currently reimbursed in Australia indicated for acute and/or chronic GVHD.

- aGVHD
    - anti-TNF antibodies
    - mTOR inhibitors
    - mycophenolate mofetil (MMF)

    - IL-2 receptor antibodies
- cGVHD
    - mycophenolate mofetil (MMF)
    - rituximab
    - calcineurin inhibitors
    - mTOR inhibitors
    - imatinib

6.2 CLINICAL CLAIM

Based on the evidence available for the proposed medical service (refer to Section 3), ECP has demonstrated encouraging response, steroids-sparing effect, QoL and overall survival in steroids-refractory/intolerant/dependent aGVHD and cGVHD. ECP is generally well tolerated with a low incidence rate of adverse events.

7 EXPECTED HEALTH OUTCOMES

7.1 EXPECTED PATIENT RELEVANT HEALTH OUTCOMES

Health outcomes will be measured in order to assess the effectiveness of the proposed intervention and appropriate comparators. Based on clinical evidence presented, primary effectiveness outcomes for the proposed intervention and comparators is response rate, which includes complete response rate, partial response rate, and overall response rate.

Second effectiveness outcomes for the proposed intervention and comparators include:

- organ-specific response rate
- reduction in steroids use
- QoL
- Survival

7.2 POTENTIAL RISKS TO PATIENTS

ECP service is well tolerated. The most common adverse event (AE) is catheter infection. Other AEs may include nausea, fever, headache, or transient arterial hypotension.

7.3 TYPE OF ECONOMIC EVALUATION

A cost-utility analysis will be conducted comparing patients treated with ECP with those treated with a basket of immunosuppressive and immunomodulatory agents. Outcomes will include incremental cost per responder, cost per life year gained and cost per QALY gained.

8 FEE

8.1 PROPOSED FUNDING TYPE

This application reflects a hybrid technology – including a medical service to be subsidised via the MBS and a drug to be subsidised via the PBS.

The integrated, closed-system ECP system incorporates integrated extracorporeal photopheresis with ultraviolet-A (UVA) irradiation in conjunction with a photoactive drug, methoxsalen, within a single device to treat GVHD. An MBS item number is sought to subsidise the delivery of the integrated, closed-system ECP service, and the PBS listing of methoxsalen is sought to reimburse the integrated drug administration during the service.

8.2 DIRECT COSTS

Direct costs associated with the integrated, closed-system ECP service are listed below, with the distinction that this listing is being made for an integrated, closed-system system rather than an open system that would incur higher direct costs and have a higher risk of adverse events [35]. It is important to note that consumables associated with delivering the integrated, closed-system ECP service are the biggest driver of costs.

Direct costs associated with the integrated, closed-system ECP service are listed as follows:

<u>Procedure</u>

- Specialist consultation

  General specialist attendance is currently reimbursed under two MBS item numbers:

  - MBS item 104: initial consultation (Fee: $85.55; Benefit: 75% = $64.20, 85% = $72.75); and
  - MBS item 105: subsequent consultation (Fee: $43.00; Benefit: 75% = $32.35, 85% = $36.55)

  The general consultation fees are likely to inform the cost for the specialist attendance requested in the management of GVHD. Frequency of subsequent haematologist consultations varies between acute and chronic GVHD as different integrated, closed-system ECP schedules are delivered to manage these two types of GVHDs. Paediatrics request more intensive follow up consultations for integrated, closed-system ECP protocol review and disease monitoring.

- Service delivery and supervision

  Indicative cost of integrated, closed-system ECP delivery and supervision is derived from the ward nursing component in the AR-DRG cost of apheresis (B62Z). The average cost of apheresis is $1,330 per DRG with an associated ward nursing cost of $164. As integrated, closed-system ECP is a more complex procedure in comparison to apheresis, the true cost is likely to be higher than $164.

<u>Pharmaceuticals</u>

- Photoactive drug methoxsalen: $125 per vial is currently charged to the ECP service and is proposed in the PBAC application as part of the co-dependent submission.

<u>Consumables</u>

The consumables used for the proposed service include an ECP tubing kit, which is estimated to be approximately $1,700 per service.

A summary of the resources to be considered in the economic analysis is presented in Table 6.

8.3 DETAILS OF PROPOSED FEE

Currently there is no MBS item number allocated to a clinical procedure similar to the integrated, closed-system ECP service. The proposed integrated, closed-system ECP service comprises three components:

1. specialist consultation as part of initial and follow-up
2. clinical supervision of integrated, closed-system ECP service delivery
3. consumables

The integrated, closed-system ECP specialist consultation fees are based on MBS items of general consultation fees MBS item 105 for subsequent consultation as patients with GVHD following allogeneic HSCT are likely to have an existing relationship with their haematologist. However, GVHD is a complicated multisystem immune-mediated disorder and is managed by highly specialised haematologists. The application of fees associated with general specialist consultation cannot fully reflect the quality of service provided in integrated, closed-system ECP specialist consultation.

The integrated, closed-system ECP service primarily includes three major steps: apheresis, drug administration and photoactivation. The integrated, closed-system ECP should be delivered by specially trained, experienced nursing staff and supervised by specialised haematologists in accredited medical centres. Currently there is only an AR-DRG code available for the reimbursement of apheresis (B62Z). As stated in Section 8.2, the estimated cost of an integrated, closed-system ECP procedure based on an apheresis procedure is considered an underestimate.

In general, an MBS item cannot include any consumables that would be reasonably necessary to perform the service. However, given the extremely high consumable cost incurred in the integrated, closed-system ECP service, and taking into account the under estimated specialist consultation fee and service delivery fee, it is expected that the inclusion of consumables in the proposed MBS fee would partially compensate those service components which are undervalued due to no matching MBS item numbers available. In addition, as advised by the Department of Health at the pre-PASC meeting, there were historical precedents which included consumables as part of the proposed MBS fee structure in the MSAC application process. In a recent report on the MBS expense trend, it is stated that “the Schedule fee for an item … takes into account of the direct and indirect costs of providing the service (eg, the length and complexity of the service, any consumables used, administrative costs, and rent for premises)” [42].

Therefore, the proposed integrated, closed-system ECP service fee would be around $1907.00 (Table 4) by summing up of subsequent specialist consultation ($43.00), integrated, closed-system ECP service supervision ($164) and consumables ($1700). The cost associated with the photoactive drug methoxsalen is to be determined via a co-dependent PBAC submission. The Sponsor remains open to further discussions with PASC and MSAC regarding this amount.

Table 3: Proposed MBS Item descriptor for integrated, closed-system ECP

Category 3 – Therapeutic procedures
MBS 38xxx INTEGRATED, CLOSED-SYSTEM EXTRACORPOREAL PHOTOPHERESIS for the treatment of steroid refractory/ dependent/intolerant acute graft-versus-host disease (grade II-IV according to modified Glucksberg criteria) and chronic graft-versus-host disease following allogeneic HSCT. Treatment includes a specialist consultation and continuous monitoring with nurse attendance under the supervision of a consultant physician. . Explanatory note (See para Tx.xx of explanatory notes for definition of steroid refractory/ dependent/intolerant acute GVHD and chronic GVHD) Fee: $1907.00 Benefit: 75% = $1430.25 85% = $1620.95

Explanatory note

steroid refractory/ dependent/intolerant acute GVHD

- Steroid-refractory cGVHD may be defined when manifestations progress despite the use of a regimen containing prednisone at >1 mg/kg/day for at least 1 week or persist without improvement despite continued treatment with prednisone at >.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks
- Steroid-dependent cGVHD may be defined when prednisone doses > 0.25 mg/kg/day or > 0.5 mg/kg every other day are needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least 2 occasions, separated by at least 8 weeks. These suggested dose thresholds match the average doses from 3 months onward in a prospective study of first-line treatment
- Steroid-intolerant cGVHD defined as patients with cGVHD who are unable to tolerate the side effects of adequate doses of systemic steroids

steroid refractory/ dependent/intolerant chronic GVHD

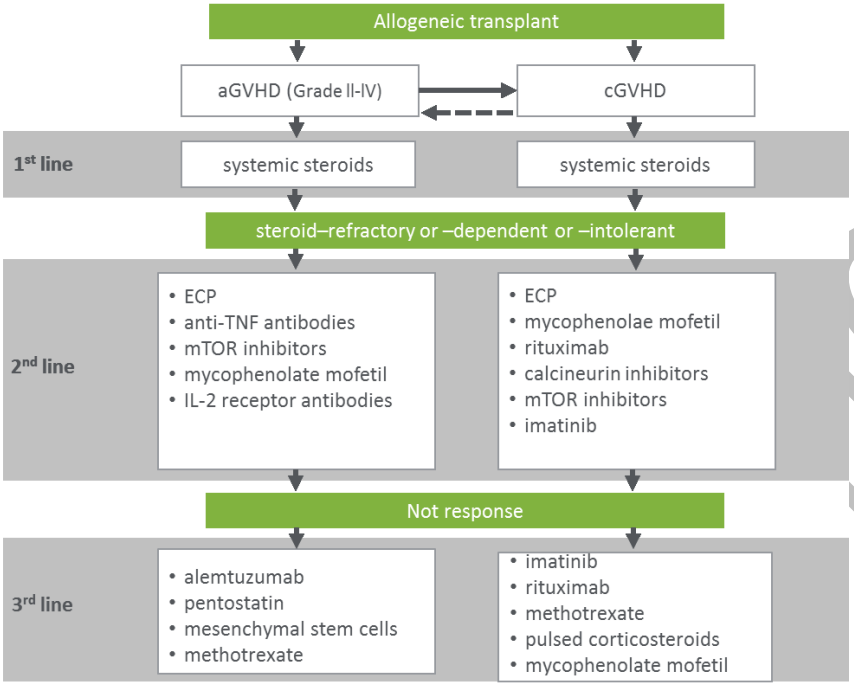
- Steroid-refractory aGVHD is defined as worsening of aGVHD after 3 days of systemic corticosteroids (minimum dose of 1 mg/kg) or no improvement after 7 days of systemic corticosteroids (minimum dose of 1 mg/kg).
- Steroid-dependent aGVHD is defined as recurrence of aGVHD (grade II or higher) during corticosteroid taper and before reaching 50% of initial starting dose of corticosteroids.
- Steroid-intolerant aGVHD defined as patients with aGVHD who are unable to tolerate the side effects of adequate doses of systemic steroids

9 CLINICAL MANAGEMENT ALGORITHM

9.1 CURRENT CLINICAL MANAGEMENT ALGORITHM

The current clinical treatment algorithm for acute and chronic GVHD is depicted in Figure 1.

Figure 1: Clinical treatment algorithm for GVHD



Systemic corticosteroids are recommended as the first-line therapy for patients with aGVHD (grade II–IV) or cGVHD. Second-line therapies are required for those who are refractory to or intolerant to or dependent on steroids. The recommended second-line therapies for acute and chronic GVHD are listed in Table 4.

Table 4: Recommended second-line therapies for acute and chronic GVHD

Grade II-IV aGVHD	cGVHD
• integrated, closed-system ECP • anti-TNF antibodies • mTOR inhibitors • mycophenolate mofetil • IL-2 receptor antibodies	• integrated, closed-system ECP • mycophenolate mofetil • rituximab • calcineurin inhibitors • mTOR inhibitors • imatinib

Abbreviations: aGVHD, acute graft-versus-host-disease; cGVHD, chronic graft-versus-host-disease; ECP, extracorporeal photopheresis; mTOR, mammalian target of rapamycin; TNF, tumour necrosis factor

Second-line therapies include a group of immunosuppressive and immunomodulatory agents. Due to the lack of randomised controlled studies of second-line therapy, there is a paucity of comparative data relating to efficacy and safety for therapies. Currently there is no standard second-line treatment recommended by any treatment guidelines or consensus statements. No consensus as to the order in which second-line therapies should be implemented has been reached.

During the consultation with the KOL in the management of GVHD, it is confirmed that the recommended second-line therapies are currently practiced in the Australian setting.

9.2 PROPOSED CLINICAL MANAGEMENT ALGORITHM

The proposed treatment algorithm for both acute and chronic GVHD is the same as presented in Figure 1. It is noted that none of the recommended second-line therapies is currently subsidised via PBS or MBS by the Australian government. Integrated, closed-system ECP is proposed as one of the second-line therapies recommended for both acute and chronic GVHD. This application is aiming to seek public funding for integrated, closed-system ECP via a co-dependent application in Australia. Alternative second-line agents are proposed as comparators in this application.

10 REGULATORY INFORMATION

In Australia, integrated ECP is currently registered with the Therapeutic Goods Administration (TGA) for the following indications:

- Cellex^{TM} System (system or kit) is indicated for the administration of photopheresis

The MBS item for integrated ECP sits within the TGA registration, and is therefore appropriate within this setting.

The active ingredient of the integrated ECP process is a 20 mcg/mL methoxsalen solution which is not currently registered with TGA for the proposed indication. Methoxsalen was designated an orphan drug status in October 2015 for the treatment of GVHD following allogeneic HSCT.

11 DECISION ANALYTIC

Table 5 describes the PICO criteria for the proposed medical service. Patients are reflective of the proposed patient population for the integrated, closed-system ECP service described in Section 3.2**Error! Reference source not found.**. Treatment intervention refers to the proposed integrated, closed-system ECP service for the management of both acute and chronic GVHD. Patient outcomes are reflective of the clinical evidence described in Section 3.3, including response rate, organ specific response rate, reduction in steroids use, QoL, and survival.

Table 5: Summary of PICO to define research question

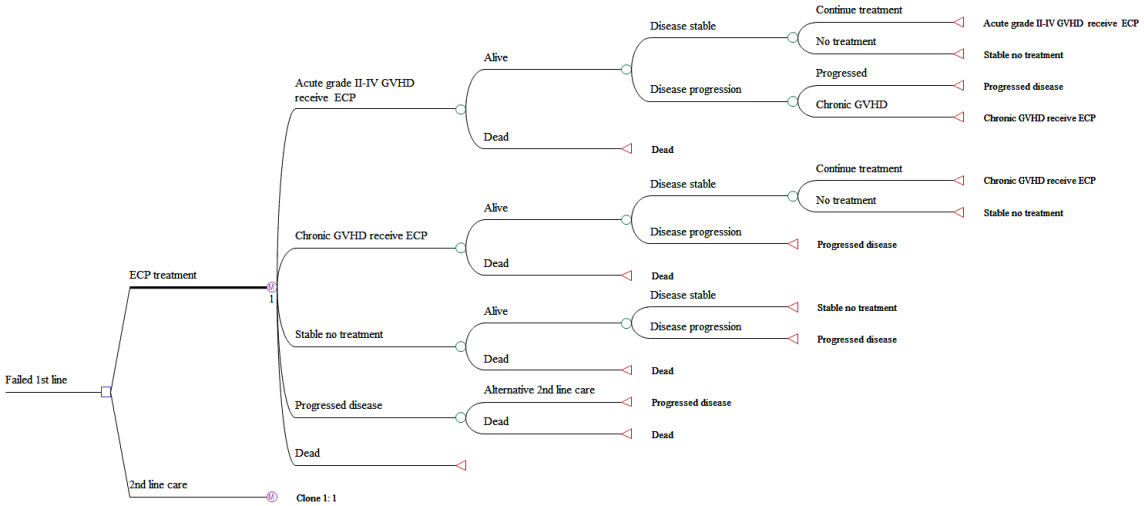
PICO	Comments
Patients	• aGVHD – patients with grade II-IV aGVHD following HSCT who are refractory to, intolerant to or dependent on steroids • cGVHD – patients with cGVHD following HSCT who are refractory to, intolerant to or dependent on steroids
Intervention	Integrated, closed-system ECP System +/- alternative second-line treatments
Comparator	• aGVHD – anti-TNF antibodies – mTOR inhibitors – MMF – IL-2 receptor antibodies • cGVHD – MMF – rituximab – calcineurin inhibitors – mTOR inhibitors

PICO	Comments
	– imatinib
Outcomes	Response rate, organ specific response rate, reduction in steroids use, QoL, survival

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; TNF, tumour necrosis factor; PICO, Population, Intervention, Comparator, Outcomes; QoL, quality of life.

The decision tree is outlined in Figure 2. The nominated 2nd line care is proposed as a basket of comparators.

Figure 2: Proposed economic model format for integrated ECP treatment



12 HEALTHCARE RESOURCES

Table 6: List of resources to be considered in the economic analysis

	Provider of resource	Code	Setting of service	Items included per Cost	Number of units of resource needed within relevant time horizon per patient receiving resource	Disaggregated unit cost					
						AR-DRG total cost	PBS Cost (DPMQ)	MBS Cost	75% benefit	85% benefit	Total cost
Resources provided beginning second-line treatment (for both proposed medical service and standard care) (OUTPATIENT TREATMENT)											
Skin test	MBS	Assumption made that skin test is two hours of specialist attendance	Private	1	1			$86.00	$64.70	$73.10	$86.00
Skin biopsy	MBS	30071	Private	1	1	-	-	$52.20	$39.15	$44.40	$52.20
Chest ultrasound	MBS	55812	Private	1	1	-	-	$109.10	$81.85	$92.75	$109.10
Chest x ray	MBS	58503	Private	1	1	-	-	$47.15	$35.40	$40.10	$47.15
Lung function test	MBS	11503	Private	1	1	-	-	$138.65	$104.00	$117.90	$138.65
Liver biopsy	MBS	30409	Private	1	1	-	-	$174.45	$130.85	$148.30	$174.45
Blood tests	MBS	65096	Private	1	1	-	-	$41.00	$30.75	$34.85	$41.00
Initial specialist attendance	MBS	104	Private	1	1	-	-	$85.55	$64.20	$72.75	$85.55
Subsequent specialist attendance	MBS	105	Private	1	1	-	-	$43.00	$32.35	$36.55	$43.00
Other resources required for proposed treatment (OUTPATIENT TREATMENT)											
Subsequent specialist attendance	MBS	105	Private	1	2	-	-	$43.00	$32.35	$36.55	$86.00
Supervising nurse attendance	AR-DRG Round 17 V6.0X Public (NURSE ATTENDANCE COMPONENT)	B62Z	Public hospital	1	2	-	-	$164.00	-	-	$328.00
Resources saved as a result of using proposed treatment (OUTPATIENT TREATMENT)											
Methoxsalen	PBS	TBD	-	-	-	-	$125	-	-	-	$125
Methotrexate - 2.5mg tablet	PBS	1622J	Public	30	-	-	$16.25	-	-	-	$0.54
Methotrexate - 10mg tablet	PBS	2272N	Public	15	-	-	$22.52	-	-	-	$1.50

	Provider of resource	Code	Setting of service	Items included per Cost	Number of units of resource needed within relevant time horizon per patient receiving resource	Disaggregated unit cost					
						AR-DRG total cost	PBS Cost (DPMQ)	MBS Cost	75% benefit	85% benefit	Total cost
rituximab	PBS	10179R	Public	-	-	-	$3120.96	-	-	-	-
imatinib	PBS	5443L	Public	-	-	-	$1862.59	-	-	-	-
mycophenolate	PBS	1836P	Public	-	-	-	$242.85	-	-	-	-
Saline solution	PBS	5212H	Private	5	2	-	$16.88	-	-	-	-
Heparin solution ampoules))	PBS	1463B	Private	50	2	-	$72.02	-	-	-	-
Adverse event costs (INPATIENT TREATMENT)											
Viral illness	AR-DRG Round 17 V6.0X Public	T63Z	Hospital	-	-	$3,128	-	-	-	-	$3,128
Other Infectious and Parasitic Diseases without complications	AR-DRG Round 17 V6.0X Public	T64C	Hospital	-	-	$4472	-	-	-	-	$4472
Stroke and other cerebral disorders without catastrophic or severe complications	AR-DRG Round 17 V6.0X Public	B70C	Hospital	-	-	$6794	-	-	-	-	$6794
Vascular Procedure Except Major Reconstruction without CPB Pump, without complication	AR-DRG Round 17 V6.0X Public	F14C	Hospital	-	-	$6960	-	-	-	-	$6960

Abbreviations: AR-DRG, Australian Refined Diagnostic Related Group; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme;
AR-DRG costs were obtained from Round 17 V6.0X Public list (Round 17 V6.0X Public list) , MBS items were sourced from the MBS website (Medical Benefits Schedule website), PBS costs are derived from the PBS website (Pharmaceutical Benefits Scheme website)

13 QUESTIONS FOR PUBLIC FUNDING

The applicant has no questions for public funding.

APPENDICES

Appendix 1

Abu-Dalle, I., et al. (2014). "Extracorporeal photopheresis in steroid-refractory acute or chronic graft-versus-host disease: results of a systematic review of prospective studies." Biol Blood Marrow Transplant **20**(11): 1677-1686.

Acute and chronic graft-versus-host disease (GVHD) remain major obstacles for successful allogeneic hematopoietic cell transplantation. Extracorporeal photopheresis (ECP) modulates immune cells, such as alloreactive T cells and dendritic cells, and improves GVHD target organ function(s) in steroid-refractory GVHD patients. We performed a systematic review to evaluate the totality of evidence regarding the efficacy of ECP for treatment of acute and chronic steroid-refractory or steroid-dependent GVHD. Nine studies, including 1 randomized controlled trial, met inclusion criteria, with a total of 323 subjects. In pooled analyses, overall response rates (ORR) were .69 (95% confidence interval [CI], .34 to .95) and .64 (95% CI, .47 to .79) for acute and chronic GVHD, respectively. In acute GVHD organ-specific responses, ECP resulted in the highest ORR for cutaneous, with .84 (95% CI, .75 to .92), followed by gastrointestinal with .65 (95% CI, .52 to .78). Similar response rates were seen in chronic GVHD involving the skin and gastrointestinal tract. Conversely, ORR for chronic GVHD involving the lungs was only .15 (95% CI, 0 to .5). In chronic GVHD, grades 3 to 4 adverse events were reported at .38 (95% CI, .06 to .78). ECP-related mortality rates were extremely low. Rates of immunosuppression discontinuation were .55 (95% CI, .40 to .70) and .23 (95% CI, .07 to .44) for acute and chronic GVHD, respectively. In summary, albeit limited by numbers of available studies, pooled analyses of prospective studies demonstrate encouraging responses after ECP treatment in acute and chronic GVHD after failing corticosteroids. Further research efforts are needed to improve organ-specific responses.

Appendix 2

See “Appendix2_KOLs discussion notes”

Appendix 3

See “Appendix 3_CELLEX operator’s manual revision 6.0 1460436”

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