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Allogeneic transplantation in transplant-naïve patients with Hodgkin Lymphoma: a single-arm, multi-centre study

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Abstract:
We evaluated the role of allogeneic stem cell transplantation in transplant-naïve patients with relapsed/refractory Hodgkin Lymphoma who had failed to achieve a metabolic complete response to 1-2 lines of salvage chemotherapy in a single-arm, open-label, multi-centre, prospective phase 2 study. Patients underwent centrally-reviewed PET-CT at study entry. Those with residual but non-progressive disease were eligible. A further 1-2 cycles of salvage were permissible in those with progressive disease or when required to arrange the logistics of the procedure, with further imaging at baseline prior to transplantation. Conditioning consisted of BCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan, and *in vivo* alemtuzumab. Donor lymphocyte infusions were administered according to a standard protocol for either mixed chimerism or residual/relapsed disease. Eleven of the 31 evaluable patients had sibling donors, 13 had HLA-matched unrelated donors, and 7 had HLA-mismatched unrelated donors. There were no graft failures, nor any cases of grade IV acute graft-versus-host disease (GvHD), with only 19.4% grade II-III, and 14.8% extensive chronic GvHD. Non-relapse related mortality was 16.1% (7.1-34.5%). Relapse incidence was 18.7% (8.2-39.2%). The study met its primary objective, with a 3-year progression free survival of 67.7% (48.4-81.2%), with equivalent survival outcomes in those with residual metabolically-active disease immediately prior to transplantation (n=24, 70.8% [17.2-83.7%]). Two of the five relapsed patients received donor lymphocytes and remain in metabolic complete response at latest follow-up, with a 3-year overall survival of 80.7% [95% CI: 61.9-90.8%]). We demonstrate encouraging results establishing a potential role for allogeneic transplantation in selected high-risk patients with Hodgkin Lymphoma.

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Abstract

We evaluated the role of allogeneic stem cell transplantation in transplant-naïve patients with relapsed/refractory Hodgkin Lymphoma who had failed to achieve a metabolic complete response to 1-2 lines of salvage chemotherapy in a single-arm, open-label, multi-centre, prospective phase 2 study (NCT00908180). Patients underwent centrally-reviewed PET-CT at study entry. Those with residual but non-progressive disease were eligible. A further 1-2 cycles of salvage were permissible in those with progressive disease or when required to arrange the logistics of the procedure, with further imaging at baseline prior to transplantation. Conditioning consisted of BCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan, and *in vivo* alemtuzumab. Donor lymphocyte infusions were administered according to a standard protocol for either mixed chimerism or residual/relapsed disease. Eleven of the 31 evaluable patients had sibling donors, 13 had HLA-matched unrelated donors, and 7 had HLA-mismatched unrelated donors. There were no graft failures, nor any cases of grade IV acute graft-versus-host disease (GvHD), with only 19.4% grade II-III, and 22.2% extensive chronic GvHD. Non-relapse related mortality was 16.1% (7.1-34.5%). Relapse incidence was 18.7% (8.2-39.2%). The study met its primary objective, with a 3-year progression free survival of 67.7% (48.4-81.2%), with equivalent survival outcomes in those with residual metabolically-active disease immediately prior to transplantation (n=24, 70.8% [17.2-83.7%]). Two of the five relapsed patients received donor lymphocytes and remain in metabolic complete response at latest follow-up, with a 3-year overall survival of 80.7% [95% CI: 61.9-90.8%]). We demonstrate encouraging results establishing a potential role for allogeneic transplantation in selected high-risk patients with Hodgkin Lymphoma.

Key points:

- PET-avidity following salvage predicts for suboptimal long-term outcomes with conventional therapies in patients with Hodgkin Lymphoma
- Allogeneic transplantation is associated with low relapse rates and encouraging longer term survival outcomes in these patients

Introduction:

Algorithms for the initial treatment of Hodgkin Lymphoma (HL) have evolved to employ response-adjusted strategies, reducing overall treatment burden whilst maintaining excellent survival outcomes. For the cohort of patients with primary treatment failure, either those with primary refractory disease or those relapsing following initial complete response, new therapies have emerged offering high response rates. Establishing how these therapies integrate into current treatment pathways remains challenging in such a rapidly evolving field. Until relatively recently, patients with relapsed/refractory disease would have received either 'full course' multi-agent chemotherapy or combined modality therapy as frontline treatment. At the point of treatment failure, they would be offered salvage chemotherapy with the aim of consolidation with autologous stem cell transplantation (ASCT). This was the established standard of care in chemo-sensitive patients based on improved progression free survival (PFS) compared to conventional chemotherapy.[1] Nevertheless, patients can be identified whose outcomes are predicted to be relatively poor following ASCT. Presentation with stage IV disease, the presence of extranodal disease, primary refractoriness, *bulk ≥5cm, ECOG performance status ≥1* or inadequate response to salvage have all been linked to worse outcomes.[2-4] Notably those with residual metabolically-avid disease assessed by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) prior to HSCT had 10-year survival of 30%, compared to 75% in those with a negative scan.[5,6] Within the latter cohort, patients with nodal-only disease in remission at the time of ASCT have an 80-90% cure rate compared to 55-65% for patients with extranodal disease.[7]

Based on these considerations we explored whether allogeneic transplantation may have a role in the management of transplant-naïve patients with residual FDG-avid disease following conventional first- or second-line salvage chemotherapy. The role of allogeneic transplantation in the management of HL remains controversial, particularly in transplant-naïve patients. The emergence of more encouraging data on allograft outcomes post-ASCT provided the rationale for evaluation earlier in the treatment pathway[8-12], allowing use of more intensive conditioning, chosen to match the standard used in the autologous setting (BCNU, etoposide, Ara-C, melphalan: BEAM) with the addition of alemtuzumab, an agent that may both disrupt the immunosuppressive tumour microenvironment that characterises HL and reduce the incidence of GvHD.[13] The latter facilitates application in the unrelated donor setting, particularly with human leukocyte antigen (HLA)-mismatched grafts. Single centre data with this approach were encouraging[13], but required confirmation in a multicentre prospective trial setting incorporating stringent quality control and central review of combined modality PET-computerised tomography (CT) imaging at baseline and post-transplant.

Methods:

Study design: The PAIReD trial (Pilot of Allogeneic Immunotherapy in Relapsed/refractory Disease; ClinicalTrials.gov identifier: NCT00908180) was conducted according to the Declaration of Helsinki and relevant International Conference on Harmonisation Good Clinical Practice Guidelines, approved by an independent national ethics committee.

Patients were required to have a confirmed diagnosis of HL, to have either primary refractory or relapsed disease failing to achieve metabolic complete response (mCR) as assessed by combined-modality PET-CT imaging following 1-2 lines of multi-agent salvage chemotherapy, and to have an HLA-compatible sibling or unrelated donor (at least 9/10 match). Patients were ineligible for trial entry if they had achieved mCR (defined as Deauville 2 or lower) or had progressive disease at the time of screening. Those with progressive disease could, however, receive a further line of salvage prior to rescreening. In view of the logistics of scheduling allogeneic transplantation, patients could receive 1-2 further cycles of salvage therapy following trial entry, using either the same regimen they had received most recently, or an alternative regimen based on clinical status. A repeat PET-CT was performed at baseline prior to allogeneic transplantation in these cases, to allow comparison post-transplant. General inclusion criteria were: age 11-65 years, WHO performance status grade 0-1, creatinine clearance >50 ml/min, cardiac ejection fraction >40%, negative pregnancy test, no relevant co-morbidities and signed informed consent. Exclusion criteria included severe hepatic impairment (serum bilirubin >1.5 times or alkaline phosphatase >2 times upper limit of normal), previous malignancy within 5 years (excluding non-melanoma skin tumour or curatively treated *in situ* carcinoma of the cervix), prior stem cell transplant or history of human immunodeficiency virus infection.

Transplantation platform: Allogeneic transplantation was performed using BEAM-Campath conditioning (BCNU [carmustine] 300mg/m^2 on day -6, etoposide 200mg/m^2 days -5 to -2, Ara-C [cytarabine] 200mg/m^2 twice daily days -5 to -2, melphalan 140mg/m^2 on day -1, and Campath-1H [alemtuzumab] 10mg intravenously on days -5 to -1). Due to global shortages in supply, 4 patients received lomustine

200mg/m^2 instead of carmustine. The graft source was mobilised stem cells (target dose $4x10^6$ $CD34^+$ cells/kg). Additional GvHD prophylaxis consisted of cyclosporine A (CsA) from day -1 with a target level of 200-300 ng/ml, tapered from day 60 post-transplant. Growth factor (Lenograstim 263mcg subcutaneously) was recommended daily from day 6 post-transplant until neutrophil recovery (>$0.5x10^9$/L). Anti-infection prophylaxis against fungi, *Varicella zoster* and *Pneumocystis (carinii) jiroveci* was given according to local standards. Surveillance for and management of other emergent infections (e.g. cytomegalovirus [CMV]) was performed according to local standards, with guidance that weekly surveillance for CMV infection should be performed for the first 3 months post transplantation.

Disease assessment and chimerism studies were performed at protocol-defined time points and donor lymphocytes infusions (DLI) administered as per standard protocol (see below).

Donor Lymphocyte Infusions: DLI were administered in 3 settings: evidence of persistent stable or increasing recipient chimerism from 6 months post transplantation and after discontinuation of CsA for 2 months; evidence of residual disease from 6 months post transplantation and following discontinuation of CsA for 2 months; evidence of disease progression or relapse at any time point post transplantation as assessed by PET-CT (Deauville 4-5), in which cases CsA was discontinued and debulking chemotherapy could be administered at the discretion of the treating physician prior to DLI. DLI were administered in an escalating dose protocol, with the initial dose determined by the indication for intervention and the donor source (Table 1). Following the initial dose further infusions were administered at 3 monthly intervals until the desired endpoint was achieved or GvHD developed. For patients

with sibling donors dose escalation proceeded according to the following schedule dependent on initial dose: 3 x 10^6, 1 x 10^7, 3 x 10^7, and 1 x 10^8 $CD3^+$ T cells/kg; whilst for patients with unrelated donors the scheduling was one increment lower: 1 x 10^6, 3 x 10^6, 1 x 10^7, 3 x 10^7 $CD3^+$ T cells/kg. DLI were not administered in the presence of active GvHD.

PET imaging: Patients underwent PET-CT scanning with low-dose unenhanced CT using full ring dedicated PET-CT cameras with quality control overseen by a core team based at University College London Hospitals NHS Trust. Subsequent PET-CT scanning for individual patients was performed under the same conditions and on the same scanner as baseline scanning. Scans were centrally reported, dictating study entry and subsequent study-directed interventions with DLI. All scans were assigned a Deauville grade. Since Deauville score in isolation gives limited information regarding overall response to intervention in those achieving less than a mCR, further response parameters were defined for the purposes of trial reporting and guidance of post-transplantation interventions. Partial response (PR) was defined as ≥50% decrease in tumour size, with residual FDG-avidity at sites of prior disease, with no increase in any mass or new mass, whilst progressive disease was defined as ≥50% increase in disease or development of new lesions that were FDG-avid. Stable disease (SD) was defined as neither PR nor progression, with FDG-avidity only at sites of prior disease. Where new PET findings may have been due to inflammatory or infective pathology, a decision on classification of disease status was made by the PET review panel and the chief investigator if biopsy of the lesion was not possible. Scans were performed at initial baseline for study entry, repeated prior to transplantation as a baseline for post-transplant comparison in those patients receiving further chemotherapy between study entry and transplantation, and then for routine

restaging at 3 and 6 months, and at 1, 2, and 3 years post-transplant. Additional scans were performed to assess response at 3 monthly intervals if patients progressed or relapsed and received further interventional therapy with DLI.

Trial end points: The primary endpoint of the study was 3-year PFS. Key secondary end points included engraftment rates, chimerism at 3 and 6 months, non-relapse-related mortality, incidence of acute and chronic GVHD, relapse rate and overall survival (OS).

Statistical methods:

The trial used an A'Hern design (one-sided 10% significance level and 80% power) aiming to show a 3-year PFS of 45%, with a lower limit for acceptability of 25%. Sample size was calculated at 26 patients, increased 32 to allow for dropouts. PFS and OS were measured from the date of transplant until the date of first progression or death (PFS) or death (OS). Patients without an event were censored at the date last seen. PFS and OS rates were calculated using Kaplan-Meier survival analysis and the cumulative incidence of relapse and non-relapse mortality (NRM) were calculated using competing risk survival analysis with NRM and relapse as competing risks respectively. All analyses were performed in STATA version 15.1 (STATACORP, Texas).

Results:

Patient characteristics: Thirty-one trial eligible patients were recruited between May 2010 and February 2014 from 8 transplant centres in the United Kingdom (Figure 1). Median age at transplant was 31 years (range 15-62 years). *Major risk factors for poor outcome are listed in Table 2*. The majority received ABVD+/-BEACOPP as first line therapy (77.4%), with smaller numbers receiving OEPA-based therapy.

First-line salvage regimens were mainly cisplatin-based (77.4%, *ESHAP or DHAP*), or ifosfamide-containing (19.3%). Two or more lines of salvage were administered in 24 (77.4%) patients prior to transplantation, with 12 (38.7%) receiving brentuximab vedotin (BV). Whilst all patients had residual FDG-avid lesions at study entry, 7 (22.6%) patients had achieved mCR immediately prior to transplantation following further chemotherapy, 15 (48.4%) achieved PR and 9 (29.0%) had SD. Median time from diagnosis to transplant was 15.9 months (range 7.5-131.1 months).

Donor characteristics: Eleven (35.5%) donors were siblings (2 mismatched at a single class I locus), 13 (41.9%) were 10/10 HLA-matched unrelated donors, and 7 (22.6%) were 9/10 HLA-mismatched unrelated donors. Of the latter, 6 were single allele class I mismatches (2A, 1B, 3C) and 1 a class II mismatch (DQ). Five mismatches were bi-directional and 2 unidirectional (1 host-versus-graft, 1 graft-versus-host). In 18 cases both donor and recipient were CMV seronegative, in 10 both were seropositive, and in 1 the donor was seropositive and the recipient seronegative.

Engraftment, non-relapse-related mortality and GvHD: Twenty-seven patients survived until day 100. There were no cases of graft rejection or secondary graft failure. Delayed engraftment (beyond 28 days to neutrophils $>0.5x10^9$/L or platelets $>20x10^9$/L)) was only reported in the platelet lineage and occurred in 5 cases (range 42-356 days). Five patients died due to non-relapse-related mortality, giving a 3-year cumulative incidence of 16.1% (95% confidence interval (CI): 7.1-34.5%, Figure 1). Four had unrelated donors (2 matched, 2 mismatched) and 1 a sibling donor. Four died prior to day 100, 3 with respiratory failure/infection as a major contributing factor and one with unexplained acute hepatic failure at day 20 (no evidence of GvHD). The latest NRM death occurred at 8.8 months. *This patient developed grade*

III acute GvHD, followed by extensive chronic GvHD affecting the gastrointestinal tract, treated with systemic steroids. She developed multiple viral infections including both cytomegalovirus and BK virus, receiving initially foscarnet and then cidofovir, with subsequent deteriorating renal function. Renal biopsy was consistent with BK nephropathy, and she died of progressive renal and multi-organ failure. Acute GvHD grades II-III occurred in 6 (19.4%) patients. *Of these, four developed grade II [12.9%] GvHD (1 isolated cutaneous involvement, 2 with cutaneous and gastrointestinal tract involvement, and 1 with cutaneous, gastrointestinal and liver involvement), and 2 grade III [6.5%](both involving cutaneous and gastrointestinal systems).* There were no cases of grade IV GvHD. Extensive chronic GvHD occurred in 6/27 (22.2%) of patients surviving beyond 100 days post transplantation, though none remain on immune suppression at latest follow-up.

Adverse events: All patients experienced at least one grade 3 adverse event (AE), most commonly relating to cytopenias in keeping with the treatment modality. Of the non-haematological AEs, the commonest related to gastrointestinal disorders (mucositis 51.6%, diarrhoea 25.8%, nausea 6.5%) and infections (overall 45.2%, neutropenic sepsis 32.3%, fungal infection 9.7%). One patient (3.2%) developed a pericardial effusion, and 2 (6.5%) developed reversible posterior leukoencephalopathy syndrome secondary to cyclosporin use. All 3 remain alive and progression free.

Chimerism: All 27 patients who survived until day 100 had chimerism performed at least once. The median time to first test was 99 days, at which point 14 were full donor and 13 mixed chimeras. Four converted to full donor status following immune suppression withdrawal, and seven following DLI (5 after a single dose, and 2 after 2

doses). Of the remaining 2, one had progressive disease at 6.2 months and died at 7.7 months from disease after receiving a single dose of BV; the other progressed at 5.9 months, received 3 doses of DLI, and is currently alive and subsequently progression-free 3 years post-transplant (remaining a mixed chimera).

Relapse and survival outcomes: Five patients had disease relapse/progression, giving a 3-year cumulative relapse incidence of 16.1% (95% CI: 7.1-34.5%), and a 3-year progression free survival rate of 67.7% (95% CI: 48.4-81.2%, Figure 2a-b). Notably, 24 patients had residual disease at the time of transplantation. Their outcomes appeared no worse than those who had achieved mCR, with a 3-year PFS of 70.8% (95% CI: 48.4-84.8%, Figure 2c). Only one patient with relapse has died. One received DLI only and achieved mCR as previously noted. One relapsed at 10.7 months and received salvage chemotherapy followed by DLI, achieving mCR maintained at latest follow up (46.9 months). One relapsed at 6.9 months, received a combination of BV and bendamustine, and remains free from further relapse at 48.3 months. The final patient relapsed at 6.0 months, received radiotherapy, and remains progression free at 35.5 months. Thus 25 patients remain alive at latest follow-up (3-year overall survival 80.7% [95% CI: 61.9-90.8%], Figure 2d), 21 of whom remain event free and 4 in complete remission following further salvage.

Discussion:

The most appropriate therapeutic strategy for patients with relapsed/refractory HL failing to respond adequately to initial salvage remains unclear. Our data help to inform this debate and represent the only prospective multicentre trial experience of a modern allogeneic transplant platform in a transplant-naïve population. By comparison, 86% of the patients on HDR-ALLO prospective study had relapsed

following a prior ASCT.[12] Although ours was a relatively small study, the data support the outcomes reported in single centre retrospective cohorts. They confirm that by using a more intensive T-deplete transplant platform it is possible to combine relatively low procedural mortality (NRM 16.1%) with an encouragingly low relapse incidence (16.1% at 3 years), to achieve a 3-year PFS of 67.7% (48.4% -81.2%). Procedural mortality and ongoing morbidity are both important factors when considering alternative treatment options for these patients. Notably, more severe (Grade III-IV) GvHD occurred in only 2 (6.5%) of the patients, and extensive chronic GvHD in 6 (22.2%) despite inclusion of 20 (64.5%) unrelated donor transplants, and 9 (29.0%) HLA-mismatched donors. Furthermore, no surviving patient remains on immune suppression.

Putting these data in the context of current clinical practice remains challenging. The study design was informed by data on ASCT outcomes in patients with FDG-avid disease following a single line of salvage[6], pre-dating data suggesting similar outcomes for those who achieve mCR following one or two lines of salvage.[14,15] Our hypothesis was that improving PFS outcomes in this cohort to 45% or greater would be clinically valuable, and by those criteria the trial met its primary endpoint. Emergent data clearly suggest, however, that patients achieving mCR following a second line of salvage may be better candidates for ASCT.[14,15] The majority of patients in the current study (n=24, 77.4%) were transplanted with residual metabolically active disease, with no evidence of inferior outcomes (3-year PFS 70.8%), supporting our prior demonstration that PET-avidity prior to allogeneic transplantation has much less prognostic significance than in the setting of ASCT.

For patients with residual disease following 2 lines of salvage there are multiple clinical options. Firstly, response could be consolidated with ASCT alone, accepting that the majority will relapse and require further therapy.[6,14,15] Outcomes of allogeneic transplantation in this setting of relapse following ASCT are generally less good. In the HDR-ALLO study 15% of patients failed to respond to salvage, and in those proceeding to allogeneic transplantation relapse incidence was 59% (55-63%) and 4-year PFS 24% (22-27%).[12] Outcomes were particularly poor in those transplanted with stable disease, where the relapse incidence was over 80%, and best in those transplanted in CR, where 4-year PFS was 50% (47-53%). Secondly, a further line(s) of salvage could be given with the aim of achieving mCR, on the assumption that ASCT outcomes would be similarly favourable regardless of number of lines of therapy required to achieve mCR. Whilst this may be the case, the number of patients achieving this level of response would be relatively small, as most will have already received BV. It is likely these patients would be considered for an checkpoint inhibitor targeting the PD1:PD-L1 axis. Response rates with these are encouraging, though most are partial, and there is currently no consensus on the role, timing and outcomes of ASCT in these patients, with many favouring the idea of ongoing treatment to progression rather than consolidation. The majority of such patients will progress within 18 months, and the impact on subsequent attempts at salvage and transplantation remain unknown. *Since our study did not include any patients who had received these agents prior to allograft it will be important to establish whether results of allograft in this patient group remain comparable to those demonstrated in the current study, or potentially are adversely impacted. Early experience of use either prior to or following allogeneic transplantation has indicated a possible impact on risk of GvHD or sinusoidal obstruction syndrome[16-18], though it is notable that*

most of this experience is reported in the setting of T-replete transplants and toxicity may potentially modulated or abrogated by the incorporation of T-cell depleting serotherapy such as alemtuzumab. Thirdly, response could be consolidated by ASCT with post-ASCT BV based on the AETHERA trial outcomes.[19,20] Notably, these outcomes were delivered in the context of BV-naïve patients and it is likely that patients failing to achieve mCR with BV prior to ASCT will gain less benefit. Our data support consideration of a fourth alternative, demonstrating the feasibility of delivering encouraging survival outcomes using a T-cell-depleted allogeneic transplant platform. Early mortality is undeniably higher with this approach, but relapse incidence remarkably low. Whilst we would not, therefore, recommend this approach for patients achieving mCR, the encouraging outcomes in the cohort transplanted with residual FDG-avid disease suggest that further exploration of this strategy is worthwhile in the higher risk patients (extranodal disease, primary refractory disease, stable disease post salvage, failure to achieve mCR with prior BV therapy) whose outcomes with alternative strategies remain suboptimal.

Authorship: EDG, NR, DCL and KSP designed the research. EDG, KT, AB, AC, SM, NR and KSP acted as PI/SUB-I on the clinical study. IK performed the central PET-CT reviews. LCH, PP, NEM and AL performed the trial data collection/analysis/oversight. AAK was the trial statistician. KSP wrote the manuscript. All authors review and commented on the manuscript. None of the authors has any conflict of interest to declare.

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Table 1: Starting dose for DLI, depending upon indication and donor source

Indication		**Sibling donor**	**Unrelated donor**
Mixed chimerism		1 x 10^6 $CD3^+$ T cells/kg	$5x10^5$ $CD3^+$ T cells/kg
Stable residual disease		1 x 10^6 $CD3^+$ T cells/kg	$5x10^5$ $CD3^+$ T cells/kg
Progression	at <12 months	3 x 10^6 $CD3^+$ T cells/kg	$1x10^6$ $CD3^+$ T cells/kg
	at >12 months	1 x 10^7 $CD3^+$ T cells/kg	

Table 2: Patient characteristics – risk factors for poor outcome

Factor	***Incidence***
Stage IV disease	*10/31 (32.3%)*
*Primary refractory disease**	*10/31 (32.3%)*
Extranodal disease	*16/31 (51.6%)*
≥3 lines of prior treatment	*24/31 (77.4%)*
Metabolically active disease at transplant	*24/31 (77.4%)*
WHO performance status: 0	*29/31 (93.5%)*
1	*2/31 (6.5%)*

** Median time from diagnosis to relapse in the cohort of 21 patients with relapsed disease was 10.5 months (range 3.4-121.9 months)*

Figure legends:

Figure 1. CONSORT diagram. NRM, non-relapse-related mortality

Figure 2. Survival outcomes. (a) Progression free and (b) overall survival for the cohort of 31 patients. (c) Progression free survival according to pre-transplant disease status. (d) Non-relapse-related mortality and (e) relapse incidence.

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Figure 1: CONSORT diagram

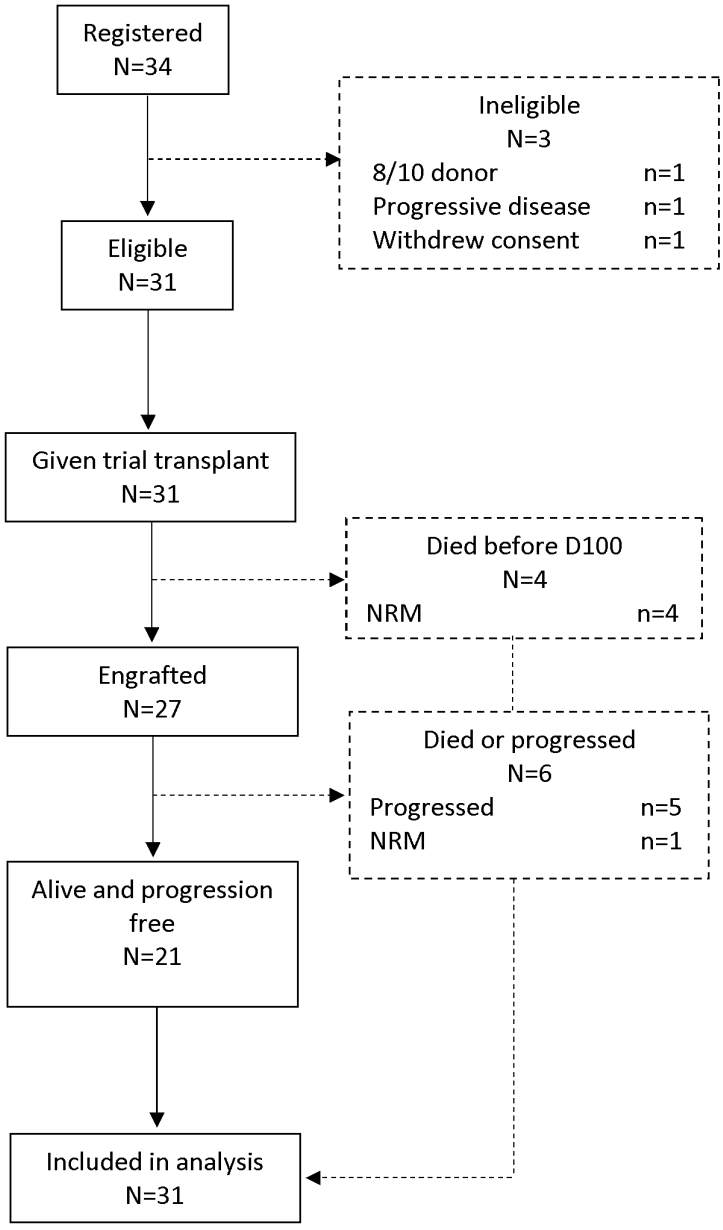
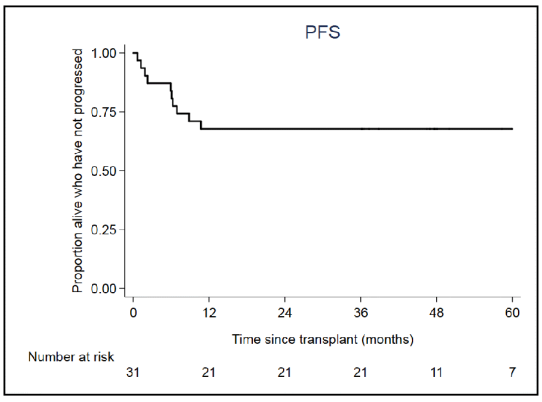


Figure 2. Survival outcomes

(a)



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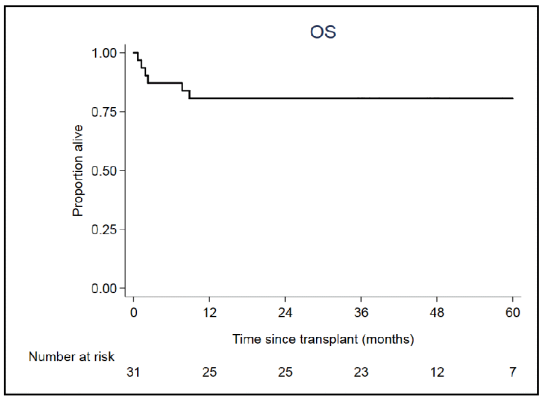
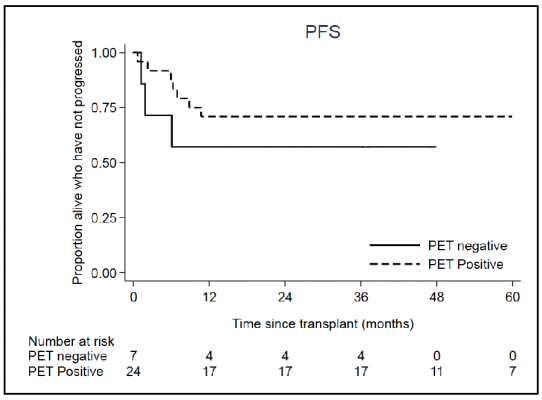
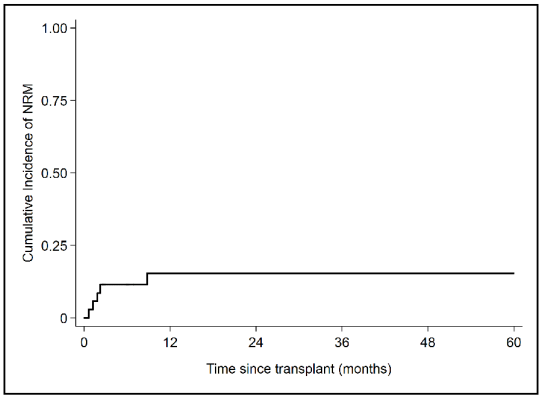


(c)



(d)



(e)