# Brentuximab-vedotin and bendamustine for relapsed or refractory Hodgkin lymphoma: the LYSA real-world experience

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**Supplemental table 1** : details of first line therapy of the study population

| First line regimen | | N = 222 |
|---|---|---|
| ABVD based | | 139 |
| BEACOPP based | | 33 |
| Other | PVAG/PVAB | 13 (12/1) |
| | Nivolumab + Vinblastin | 3 |
| | Bv-based (Bv-AVD/Bv-DHA) | 2 (1/1) |
| | Platinum-based (DHAP, DHAOx) | 3 (2/1) |
| | EBVP | 1 |
| | COPP-ABV | 1 |
| | VABEM | 1 |
| | ACVP/HD-MTX/Holoxan-VP16/HDAC | 1 |
| | R-CHOP | 1 |
| Not known | | 24 |

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine, ; ACVP : doxorubicin, cyclophosphamide, vindesine, prednisone ; Bv: brentuximab-vedotin; BEACOPP: escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP-ABV : cyclophosphamide, prednisone, procarbazine, adriamycin, bleomycin, vinblastine ; DHAP/OX : dexamethasone, high dose cytarabine, cisplatin/oxaliplatin EBVP : epicirubicin, bleomycin, vinblastine, prednisone ; PVAG/PVAB : prednisone, vinblastine, doxorubicin, gemcitabine/bendamustine ; R-CHOP : rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone ; VABEM : vindesine, doxorubicin, carmustine, etoposide, methylprednisolone

**Supplemental table 2** : risk factors for PFS in multivariable analysis when response on interim PET is considered.

| Parameter | Modality | Univariate | | Multivariable | |
|---|---|---|---|---|---|
| | | HR | p-value | HR | p-value |
| ECOG | 0-1 | 1 | | 1 | |
| | 2-4 | 2.34 (1.1-5.0) | 0.0260 | 2.22 (1.0-4.8) | 0.0438 |
| Ann Arbor stage | 3-4 | 2.93 (1.5-5.7) | 0.0013 | 2.30 (1.2-4.6) | 0.0173 |
| Presence of symptoms | Yes | 1.17 (0.6-2.2) | 0.61 | | |
| Gender | Female | 0.81 (0.5-1.4) | 0.43 | | |
| Number of previous lines | 1 | 1 | | | |
| | 2 | 2.08 (0.9-4.6) | 0.07 | | |
| | >3 | 37.54 (4.2-337.2) | 0.0012 | | |
| Disease status | Relapse | 0.82 (0.5-1.4) | 0.48 | | |
| First line treatment | ABVD based | 1 | | | |
| | BEACOPP based | 0.99 (0.5-2.1) | 0.98 | | |
| | Other | 2.21 (1.2-4.2) | 0.0156 | | |
| Delay between diagnosis and treatment | Continuous | 1.000 (0.993-1.008) | 0.89 | | |
| Eligible for ASCT | No | 2.88 (1.7-4.8) | <0.0001 | 3.23 (1.9-5.6) | <0.0001 |
| Deauville score | 1/2/3 | 1 | | 1 | |
| | 4 | 2.70 (1.4-5.1) | 0.0020 | 2.95 (1.5-5.7) | 0.0011 |
| | 5 | 6.54 (3.3-12.8) | <0.0001 | 4.66 (2.3-9.4) | <0.0001 |

**Supplemental table 3 :** adverse events of interest in transplant eligible and non-eligible patients.

| | Eligible for ASCT at B2 initiation | |
|---|---|---|
| | **No (n = 72)** | **Yes (n = 150)** |
| **Red blood cell transfusion** | | |
| No | 65 (90.3%) | 145 (96.7%) |
| Yes | 7 (9.7%) | 5 (3.3%) |
| **Platelet transfusion** | | |
| No | 68 (94.4%) | 144 (96.0%) |
| Yes | 4 (5.6%) | 6 (4.0%) |
| **Non hematological toxicity grade ≥ 3** | | |
| No | 46 (63.9%) | 123 (82.0%) |
| Yes | 26 (36.1%) | 27 (18.0%) |
| **Infection grade ≥ 2** | | |
| No | 53 (73.6%) | 124 (82.7%) |
| Yes | 19 (26.4%) | 26 (17.3%) |
| 2 | 6 (8.3%) | 11 (7.3%) |
| 3 | 8 (11.1%) | 12 (8.0%) |
| 4 | 1 (1.4%) | 1 (0.7%) |
| 5 | 4 (5.6%) | 2 (1.3%) |
| **Peripheral neuropathy** | | |
| No | 57 (79.2%) | 122 (81.3%) |
| Yes | 17 (21.8%) | 28 (18.7%) |
| 1 | 9 (12.5%) | 15 (10.0%) |
| 2 | 4 (5.6%) | 10 (6.7%) |
| 3 | 2 (2.8%) | 3 (2.0%) |
| **Digestive toxicity ≥ grade 2** | | |
| No | 57 (79.2%) | 129 (86.0%) |
| Yes | 15 (20.8%) | 21 (14.0%) |
| 2 | 10 (13.9%) | 16 (10.7%) |
| 3 | 5 (6.9%) | 5 (3.3%) |
| **Skin toxicity ≥ grade 2** | | |
| No | 57 (82%) | 132 (88%) |
| Yes | 15 (18%) | 18 (12%) |
| 2 | 6 (8.3%) | 6 (4.0%) |
| 3 | 7 (9.7%) | 12 (8.0%) |
| **Perfusion reactions ≥ grade 2** | | |
| No | 60 (83.4%) | 131 (86.0%) |
| Yes | 12 (16.6%) | 19 (14%) |
| 2 | 7 (9.7%) | 14 (9.3%) |
| 3 | 5 (6.9%) | 6 (4.0%) |
| 4 | 0 (0.0%) | 1 (0.7%) |
| **Number of days for hospitalization** | | |
| Median (IQR) | 0.0 (0-3) | 0.0 (0-0) |

**Supplemental table 4 :** reason for treatment reduction or discontinuation in the study cohort

| | All (n = 222) | Eligible for ASCT at treatment initiation | |
|---|---|---|---|
| | | No (n = 72) | Yes (n = 150) |
| **Dose adaptation for bendamustine** | | | |
| No | 158 (71.2%) | 40 (55.6%) | 118 (78.7%) |
| Dose reduction | 34 (15.3%) | 19 (26.4%) | 15 (10.0%) |
| Permanent stop | 30 (13.5%) | 13 (18.1%) | 17 (11.3%) |
| **Reason of dose adaptation for bendamustine** | | | |
| Hematologic toxicities | 8 (3.6%) | 3 (4.2%) | 5 (3.3%) |
| Other toxicities | 36 (16.2%) | 20 (27.8%) | 16 (10.6%) |
| Cutaneous toxicity / perfusion reaction | 23 (10.4%) | 10 (13.9%) | 13 (8.7%) |
| Digestive toxicity | 6 (2.7%) | 4 (5.5%) | 2 (1.3%) |
| Infection | 1 (0.4%) | 0 | 1 (0.6%) |
| Frailty | 6 (2.7%) | 6 (8.3%) | 0 |
| Logistical (harvesting, ASCT, COVID pandemia) | 8 (3.6%) | 1 (1.4%) | 7 (4.7%) |
| Unknown | 14 (6.3%) | 10 (13.8%) | 4 (2.7%) |
| **Dose adaptation for Bv** | | | |
| No | 186 (83.8%) | 58 (80.6%) | 128 (85.3%) |
| Dose reduction | 20 (9.0%) | 11 (15.3%) | 9 (6.0%) |
| Permanent stop | 16 (7.2%) | 3 (4.2%) | 13 (8.7%) |
| **Reason of dose adaptation for Bv** | | | |
| Hematologic toxicities | 4 (1.8%) | 0 | 4 (2.7%) |
| Other toxicities | 23 (10.3%) | 8 (11.1%) | 15 (10%) |
| Peripheral neuropathy | 10 (4.5%) | 5 (6.9%) | 5 (3.3%) |
| Cutaneous toxicity / perfusion reaction | 5 (2.3%) | 1 (1.4%) | 4 (2.7%) |
| Infection | 3 (1.4%) | 0 | 3 (2.0%) |
| Interstitial lung disease | 2 (0.9%) | 1 (1.4%) | 1 (0.6%) |
| Digestive toxicity | 2 (0.9%) | 0 | 2 (1.3%) |
| Frailty | 1 (0.4%) | 1 (1.4%) | 0 |
| Logistical (harvesting, ASCT, COVID pandemia) | 1 (0.4%) | 0 | 1 (0.6%) |
| Unknown | 8 (3.6%) | 6 (8.3%) | 2 (1.3%) |

ASCT: autologous stem cell transplantation; Bv: brentuximab-vedotin

**Supplemental table 5** : risk factors for all grade ≥ 3 adverse events in multivariable analysis

| Parameter | Modality | Univariate | | Multivariable | |
|---|---|---|---|---|---|
| | | OR | p-value | OR | p-value |
| ECOG | 0-1 | 1 | | | |
| | 2-4 | 2.43 (1.0-5.8) | 0.0459 | | |
| Ann Arbor stage | 1-2 | 1 | | | |
| | 3-4 | 1.20 (0.6-2.3) | 0.59 | | |
| Presence of symptoms | Yes | 1.12 (0.6-2.3) | 0.75 | | |
| Gender | Female | 1.10 (0.6-2.1) | 0.77 | | |
| Number of previous lines | 1 | 1 | | | |
| | 2 | 0.97 (0.5-2.0) | 0.93 | | |
| | >3 | 0.69 (0.2-2.0) | 0.49 | | |
| Age | Continuous | 1.033 (1.02-1.05) | 0.0003 | 1.033 (1.02-1.05) | 0.0003 |
| Number of BV cycles | Continuous | 1.05 (0.98-1.1) | 0.15 | | |

**Supplemental table 6 :** risk factors for neuropathy grade ≥ 2 in multivariable analysis

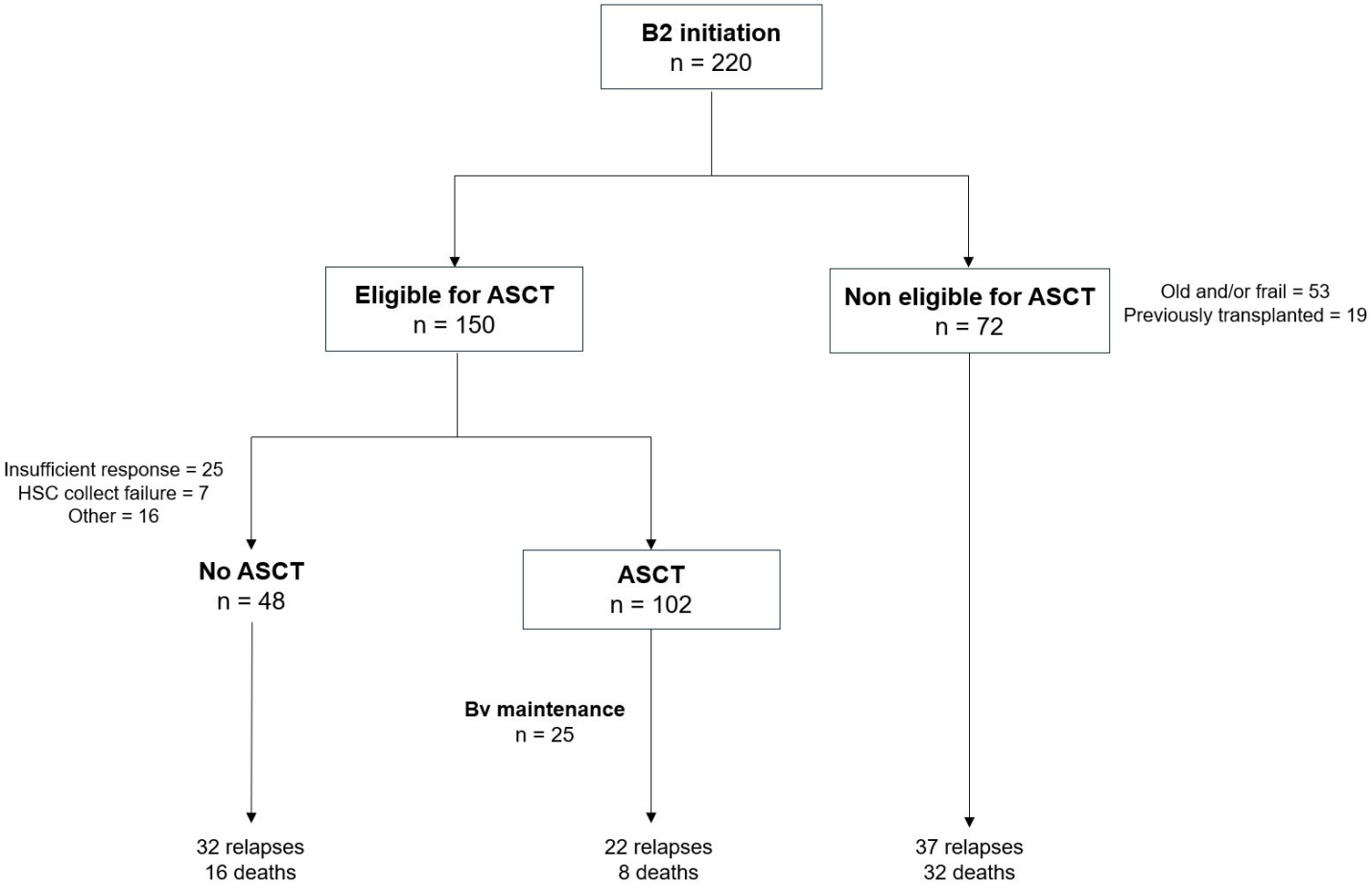
| Parameter | Modality | Univariate | | Multivariable | |
|---|---|---|---|---|---|
| | | OR | p-value | OR | p-value |
| ECOG | 0-1 | 1 | | | |
| | 2-4 | 0.41 (0.1-3.3) | 0.40 | | |
| Ann Arbor stage | 1-2 | 1 | | | |
| | 3-4 | 0.72 (0.3-1.9) | 0.59 | | |
| Presence of symptoms | Yes | 0.53 (0.1-1.9) | 0.33 | | |
| Gender | Female | 1.67 (0.7-4.3) | 0.29 | | |
| Number of previous lines | 2 | 0.99 (0.4-2.7) | 0.98 | | |
| | >3 | NA | NA | | |
| Age | Continuous | 1.011 (0.99-1.04) | 0.39 | | |
| Number of BV cycles | Continuous | 1.17 (1.1-1.3) | <0.001 | 1.17 (1.1-1.3) | <0.001 |

**Supplemental table 7** : details of second primary malignancies in the study cohort

| Age at B2 initiation | Gender | Eligible for ASCT at B2 initiation | Details of SPM | Delay between treatment initiation and SPM (months) | Death due to SPM |
|---|---|---|---|---|---|
| 39 | Male | Yes | AITL | 28.1 | No |
| 78 | Male | No | Prostatic cancer | 17.6 | No |
| 52 | Male | Yes | Small cell lung cancer | 24.8 | No |
| 53 | Male | Yes | DLBCL | 35 | No |
| 59 | Male | Yes | Prostatic cancer | 10.4 | No |
| 56 | Female | Yes | AITL | 20.9 | No |
| 71 | Female | No | MDS | 10.1 | No |
| 71 | Male | No | Urothelial carcinoma | 2.0 | No |
| 68 | Male | No | Squamous cell lung cancer | 16.0 | No |
| 72 | Male | No | Small cell lung cancer | 16.2 | No |
| 83 | Female | No | MDS | 58.6 | No |
| 25 | Male | Yes | PTLD after HSCT | 49.5 | No |
| 60 | Male | Yes | DLBCL | 21.1 | No |
| 82 | Male | No | MDS followed by AML | 17.7 | Yes |
| 69 | Male | No | Gastric cancer | 15.9 | Yes |
| 27 | Female | No | AML | 26.2 | Yes |

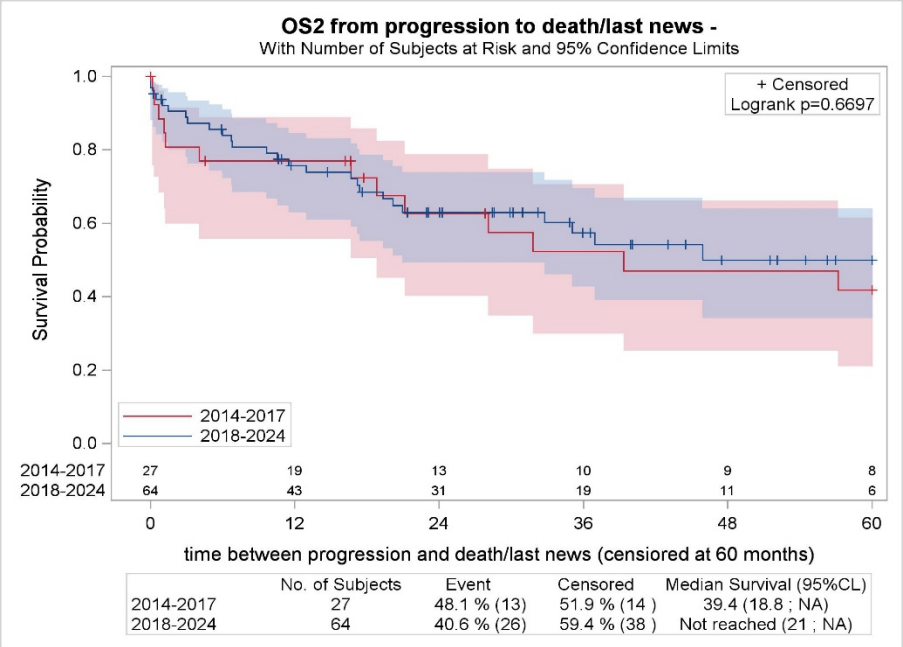
AITL: angioimmunoblastic T-cell lymphoma; AML: acute myeloid leukemia; ASCT: autologous stem cell transplantation; DLBCL: diffuse large B-cell lymphoma; HSCT: heterologous stem cell transplantation; MDS: myelodysplastic syndrome; PTLD: post-transplant lymphoproliferative disorder; SPM: second primary malignancies.

**Supplemental figure 1 :** flow chart of the study population



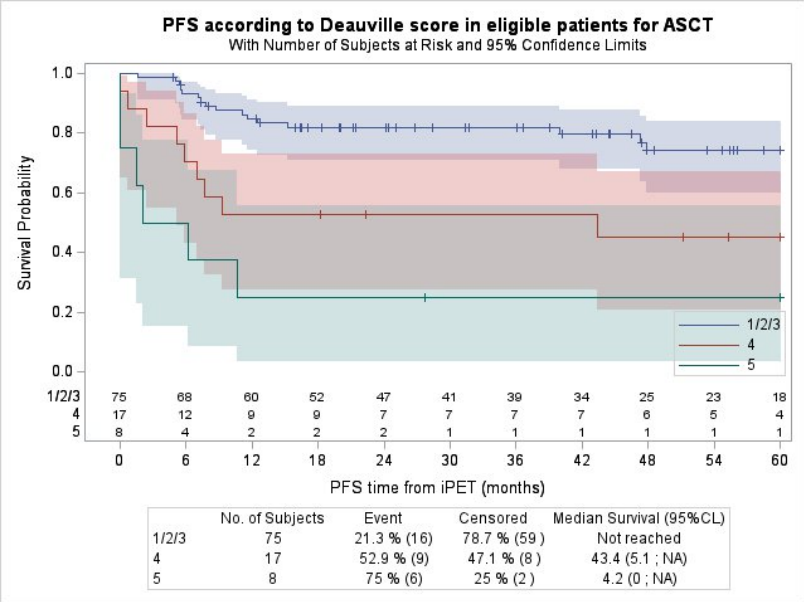

ASCT : autologous stem cells transplantation ; B2 : Bendamustine and brentuximab-vedotin ; Bv : brentuximab-vedotin ; HSC : hematopoietic stem cells

**Supplemental figure 2 :** OS2 of patients experiencing progression or relapse after B2 salvage

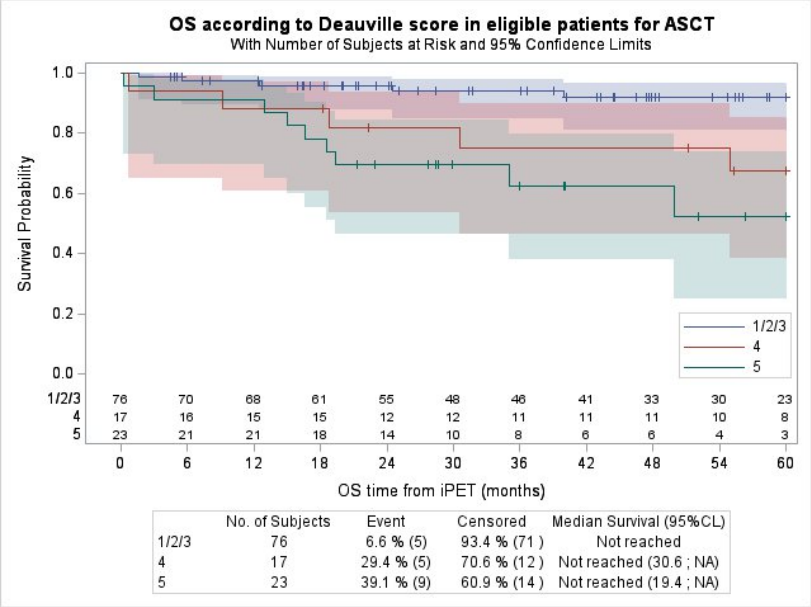


**Supplemental figure 3** : PFS (A) and OS (B) of patients eligible for ASCT stratified by early PET results

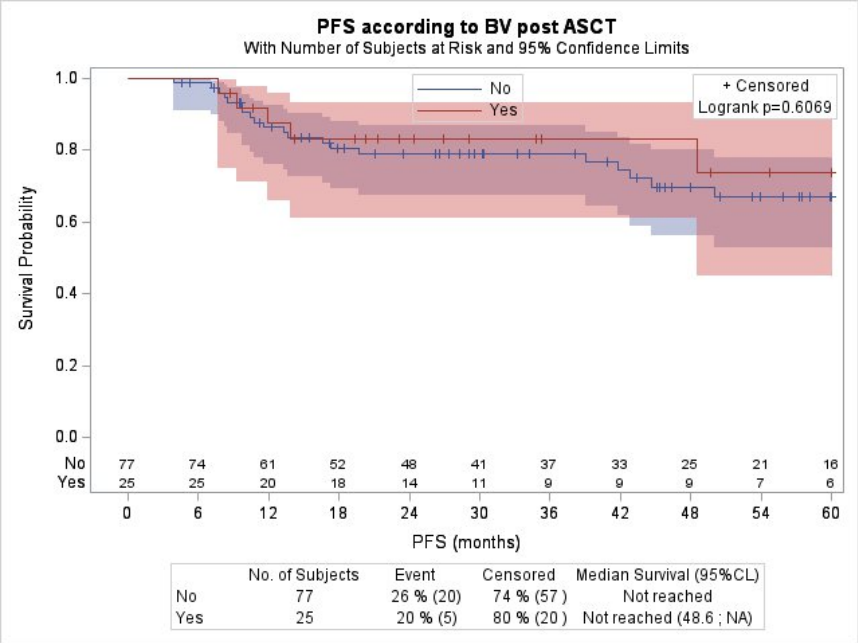
A.




B.

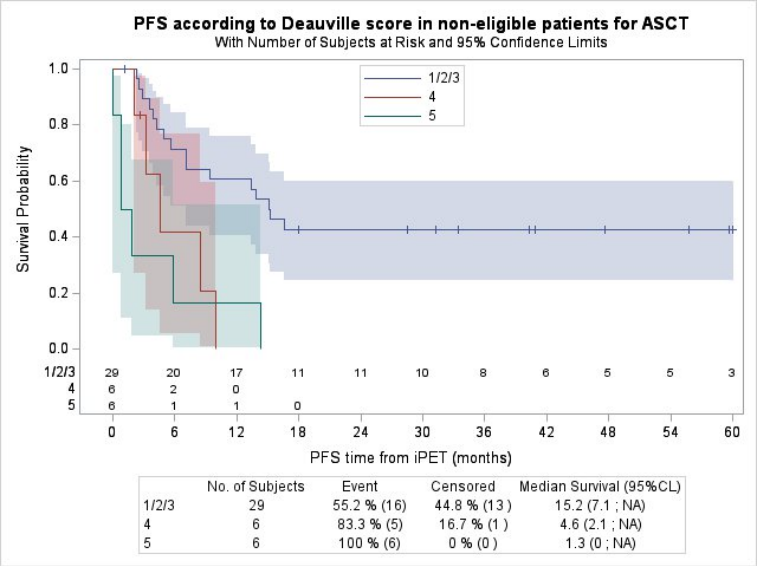


**Supplemental figure 4** : PFS of transplanted patients stratified by use of Bv maintenance



**Supplemental figure 5** : PFS (A) and OS (B) of patients non-eligible for ASCT stratified by early PET results

A.




B.

