HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2019 January ; 25(1): 94–99. doi:10.1016/j.bbmt.2018.08.028.

Significant Risk of Graft-versus-Host Disease with Exposure to Checkpoint Inhibitors Before and After Allogeneic transplantation

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Abstract

Investigators are using checkpoint inhibitors (CPI) to treat aggressive hematologic malignancies before patients undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT) and in some patients with relapsed disease after allo-HSCT. CTLA-4 inhibitors and PD-1 inhibitors are two main types of CPI, which work through activation of the immune system. On one hand CPI can achieve graft versus tumor (GVT) effect, and on the other hand there is risk of graft versus host disease (GVHD). After a comprehensive literature review we included data (n=283) from twenty-four studies (11 original manuscripts, 13 case reports or case series) and evaluated the results to assess the safety and efficacy of CPI use in conjunction with allo-HSCT. One hundred seven patients received CPI before allo-HSCT and one hundred seventy-six patients received CPI after allo-HSCT. The most common indication for CPI use was for Hodgkin lymphoma. The CPIs used in various studies included ipilimumab, nivolumab and pembrolizumab.

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Keywords

Allogeneic hematopoietic stem cell transplantation; GVHD; Ipilimumab; Nivolumab; Pembrolizumab; Outcomes

In patients exposed to CPI before allo-HSCT 56% patients developed acute GVHD and 29% patients developed chronic GVHD. Investigators reported twenty deaths, of which 60% were GVHD-related. The overall mortality risk with GVHD is 11%. In this group, investigators noted objective response rate (ORR) in 68% of patients with complete remission (CR) in 47% of patients, partial remission (PR) in 21% of patients and stable disease (SD) in 11% of patients. In patients who received CPI after allo-HSCT for disease relapse, 14% of patients developed acute GVHD and 9% of patients developed chronic GVHD. Investigators reported forty deaths of which 28% were GVHD related. The mortality risk with GVHD is around 7%. Investigators reported ORR in 54% of patients with CR in 33% of patients, PR in 21% of patients and disease stabilization in 5% of patients. After careful evaluation of collective data, we found that CPI use both before and after allo-HSCT can be highly effective, but exposure can lead to a significantly increased risk of GVHD related morbidity and mortality in this patient population. Despite limited availability of data, there is need for extreme caution while making decisions regarding the use of CPI. Detailed discussion and prospective well-designed clinical trials would be required in further exploration of this issue.

Introduction:

The use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in treating aggressive hematological malignancies has potential for graft versus tumor (GVT) effect on one hand, and risk of graft versus host disease (GVHD) on the other. Despite the use of intensive conditioning followed by allo-HSCT, primary disease relapse remains one of the leading causes of death (1, 2). A summary report published by the Center for International Blood and Marrow Transplant (CIBMTR) shows that patients who received transplants from matched unrelated donors (MUD) and HLA matched siblings (MRD) have relapse rates of 30% and 40% respectively. Various postulated mechanisms of disease relapse after allo-HSCT include immune escape by the tumor, T-cell anergy, down-regulation of regulatory T cells and activation of immune checkpoints. Relapse risk may also be higher with the use of non-ablative conditioning regimens (3). Tumors can use Cytotoxic T-lymphocyte associated protein-4 (CTLA-4) and Programmed Death-1 (PD1) as immune checkpoint escape mechanisms. The tumor antigens stimulate T lymphocytes to express receptors for immune checkpoints. The interaction between tumor cell ligands and checkpoint receptors prevents the T cells from full activation and proliferation (2).

Recent developments in the field of immunotherapy have led to the discovery of many checkpoint inhibitors (CPI), some of which are monoclonal antibodies directed against immune checkpoint pathways (CTLA-4 and PD-1) (4). Examples of CPI in clinical use include ipilimumab, pembrolizumab and nivolumab. Ipilimumab blocks CTLA-4 while nivolumab and pembrolizumab block PD-1 receptors. Several CPI agents have received approval and investigators are looking at additional agents as potential monotherapy or as

combination regimens in clinical trials for the treatment of relapsed or refractory hematologic malignancies. These agents are being used either before or after allo-HSCT as salvage or rescue agents for the treatment of aggressive hematological neoplasms. This CPI use has led to many serious immune related side effects (i.e., autoimmune diseases) and data is emerging on serious and potentially fatal GVHD in patients who undergo allo-HSCT (2, 4, 5). Researchers have strongly recommended starting PD-1 blockers at low doses and close monitoring of patients for signs of GVHD, when using in pre or post allo-HSCT settings for patients with relapsed or refractory classical Hodgkin lymphoma (6). There is a paucity of data on the safety and efficacy regarding the use of CPI in the peri-allo-HSCT setting. In this manuscript, our objective is to report collective data and educate the transplant community about the safety, efficacy and risks related to the checkpoint inhibitor exposure when used in allo-HSCT population.

Methods:

We completed a comprehensive data search on PubMed on 03–28-2018. Our search strategy included MeSH terms and key words for allogeneic hematopoietic stem cell transplant, checkpoint inhibitors including trade names and generic names, graft versus host disease, safety and efficacy. We found 123 articles and after screening for duplicates, review articles and nonrelevant studies, we selected twenty-four articles (13 case reports and 11 original manuscripts) for data extraction. Our inclusion criteria included an analysis of checkpoint inhibitors utilized in hematological malignancies either before or after allo-HSCT. We manually extracted data and summarized our results in the tables (Table 1, 2, 3) and divided patients into two groups based on whether CPI agents were used before or after allo-HSCT, and evaluated studies particularly for GVHD (acute and chronic), mortality data, and objective response rate.

Results:

We reported data from 11 published original articles (1, 2, 5, 7–14) and thirteen case reports/ case series (15–27), which include data on 283 patients. Nivolumab, pembrolizumab and ipilimumab were various CPI agents used either alone or in combination.

Indications:

Hodgkin’s lymphoma (HL) was the most common indication (n=93) in patients receiving CPI before allo-HSCT. Other indications included non-Hodgkin’s lymphoma (NHL) (n=10), myelodysplastic syndrome (MDS) (n=3) and T cell lymphoma (n=2).

The most common indication in patients receiving CPI after allo-HSCT was HL (n=89). Other indications include AML (n=28), NHL (n=15), MM (n=9), CLL (n=7), NK/T-cell lymphoma (n=7), MDS (n=4), ALL (n=4), CML (n=2), CMML (n=2), ALCL (n=2), concurrent HL & NHL (n=1) and one case each of myeloproliferative disorder, renal cell carcinoma, breast carcinoma, non-small cell lung carcinoma, mesothelioma, and desmoplastic small round cell carcinoma.

Original Articles:

1) Prior to allo-HSCT:

a) CPI used and their doses: In total, 107 patients were given CPI before allo-HSCT. Ninety-one patients received nivolumab for a median number of cycles ranging from four to eleven. Out of these ninety-one, thirty-seven patients received nivolumab at the dose of 3 mg/kg; dosage information is not available for the rest. Pembrolizumab was given to eleven patients for 8 cycles; no information about dosage was mentioned. A median of four cycles of ipilimumab were administered in eight patients; no dose was mentioned.

b) Efficacy and Safety: Investigators noted ORR in 42 of 62 patients (68%) with CR in 29 patients (47%) and PR in 13 patients (21%). Investigators noted stable disease (SD) in 7 patients (11%) while 12 patients (19%) were reported to have progressive disease (PD). In this group, in which patients received CPI before allo-HSCT, eight (7%) patients developed hyper-acute GVHD; sixty (56%) patients developed acute GVHD while 20 out of 70 reported patients (29%) developed chronic GVHD. Investigators reported 20 deaths, of which 12 deaths (60%) were GVHD related.

2) Post allo-HSCT:

a) CPI used and their doses: One hundred fifty patients received CPI after an allo-HSCT. Sixty-two patients received nivolumab therapy with a dose of 3 mg/kg, every two weeks in two studies for eight (8) and two(7) cycles, respectively, and 1 mg/kg every two weeks for 8 cycles in the third study (13). Eighty-five patients received ipilimumab therapy. In one study, single infusions were given to twenty-nine patients; starting with a dose of 0.1 mg/kg and increased to 0.33, 0.66, 1.0 and 3.0 mg/kg (1). In another study, six patients received a dose of 3.0 mg/kg and twenty-two patients received a dose of 10 mg/kg for four cycles followed by maintenance therapy every 12 weeks for a year. Another cohort of 15 patients received ipilimumab at the dose of 5 mg/kg (2, 13). Ipilimumab was given to 10 patients at 3 mg/kg for a total of 2 doses, alternating with lenalidomide (9). In another study, 3 patients received ipilimumab for five cycles with no information available on the dose (12). A total of four patients received pembrolizumab. Three patients received a dose of 200 mg/kg every 3 weeks with the median of 2 cycles (7). The fourth patient received the drug in 5 cycles and no information was given on dosage (12).

b) Efficacy and Safety: A total of 19 patients who received CPI post-transplant developed acute GVHD (13%) while 11% developed chronic GVHD. Out of a total of 123 evaluable patients, ORR was seen in 59 patients (48%) with 34 patients (28%) achieving CR while 25 (20%) patients achieved PR. Stable disease (SD) was noted in 7 patients (6 %) while 4 patients (3%) developed disease progression. Investigators reported 35 deaths of which, 10 cases (28%) were GVHD related. Nine studies reported prior history of GVHD in 49% patients (1, 7–9, 13, 16, 20, 26, 27). Complications, other than GVHD, include hematologic side effects (22%), most notably neutropenia; followed by respiratory and hepatic complications (16% and 14% respectively).

Case reports/Case series:

1) Post allo-HSCT:

a) CPI used and their doses: A total of 26 patients received CPI therapy after allo-HSCT as salvage therapy for different hematological malignancies. Twelve patients (46%) were treated with pembrolizumab (PD-1 blockade), three with a dose of 2.0 mg/kg every 3 weeks and two with a single dose therapy (3.3 mg/kg; not mentioned). The other fourteen patients (54%) were treated with nivolumab (PD-1 blockade), two with a single infusion at 3 mg/kg (27), two patients with six and four cycles (dose not mentioned) respectively (26). Two patients received a single dose of 100 mg (25) and 200 mg (24), two were treated with a single 3 mg/kg dose, one with two doses of 100 mg (25) two weeks apart, two cases with thirteen (23) and sixteen (20) cycles of 3 mg/kg every two weeks, one case with seven cycles of 2 mg/kg every two weeks (16), two cases with seven (19) and sixteen cycles (16) of 2 mg/kg every three weeks respectively. One case treated with five weekly doses of 0.3–1.0 mg/kg (25) and two patients with an escalating dosage of 0.5 to 3 mg/kg (15) and 0.5 to 2.0 mg/kg(18) for up to six doses.

b) Efficacy and Safety: At the time of observation of respective cases, investigators recorded an ongoing response in fifteen (58%) patients with CR, seven cases (30%) with PR, one case (4%) with stable disease and one case (4%) with progressive disease. One patient (4%) could not be evaluated for an outcome. Five patients (19%) developed acute GVHD and another patient (4%) had a flare of existing GVHD. Total mortality was 15%; one case (4%) died due to GVHD and the other three deaths were due to pneumonia, hepatic failure and fungal infection respectively. Most common adverse reactions noted were related to gastrointestinal tract notably hepatitis (32%), followed by skin (25%) and pulmonary related problems (25%).

Discussion:

A hundred and seven patients from seven studies (5, 10–12, 14, 26, 27) revealed an overwhelming rate of acute GVHD (56%) among patients who were exposed to CPI therapy prior to receiving allo-HSCT. This rate is higher than the historical incidence that ranges between 26% to 50% (28, 29). Most studies used nivolumab for their patients, while only one study used pembrolizumab in eleven patients(5) and another one used ipilimumab for eight patients (12). Twelve of the twenty (60%) deceased patients died due to GVHD, and aggregated mortality risk attributed to GVHD was 11%, which may be higher than historically reported incidence (8%−10%) but statistical significance is not proven (30). Hyper-acute GVHD (diagnosed within 14 days after transplantation) occurred in eight cases (7%), suggesting a higher risk of hyper-acute GVHD with the use of CPI therapy prior to allo-HSCT. The median interval between exposures to the last dose of CPI and allo-HSCT was variable ranging between 28 and 62 days. The half-life of nivolumab is about a month. The high incidence (56%) of GVHD among studies is probably secondary to donor derived lymphocyte activation with residual CPI lasting in the body after allo-HSCT resulting in higher incidence of hyper-acute, atypical non-infectious febrile syndrome and acute GVHD. Decreased PD-1 expression on T-cells persists for at least 10 months following CPI therapy which confirms the long term immune activation beyond many half-lives (5). Due to the

long-lasting effects of CPI on immune activation, the time duration needed for GVHD risk to return to baseline is unknown in this patient population. We compared the studies with shortest median intervals (28 (11), 29 (14), 30 (10) days) and longest median intervals (43 (12), 44 (27), 62 (5) days) between the last dose of CPI and allo-HSCT. We found that the incidence of GVHD was 60% versus 70%, but the number of patients in each group was very limited. Increased rate of efficacy with GVT effect correlated positively with increasing risk of GVHD activity (grade 2–4) in three studies (5, 10, 27), complementing the association between GVT and GVHD, as previously reported in animal studies which tested PD-1 blockade (31, 32). US Food and Drug Administration (FDA) has issued label warnings for use of HSCT after prior PD-1 blockade. Immunosuppressive CD4+ T regulatory cells with CTLA-4 expression have been found in markedly high proportions surrounding malignant tissues (33). This may explain the increased efficacy as well as high incidence of GVHD associated with checkpoint inhibitors use as PD1 blockade depletes the PD1+ T cells, and T reg population. CD62L is a lymph node “homing receptor” that is down regulated during T-cell response that allows for escape of T-lymphocytes from lymph nodes. Ipilimumab indirectly increases the number of CD62L(–) regulatory CD4+ cells (2). PD-1 blockade may alter post allo-HSCT immune reconstitution through its effects on antigenpresenting cells (APC) and cytokines (5). Three of the included studies reported increased numbers of circulating, activated CD8+ and CD4+ cells but a decreased CD4+ Treg:Teff ratio (2, 5, 33). A CD4+ Treg:Teff ratio of less than 9% is associated with increased incidence and severity of GVHD. In one study where CPI was used this ratio was found to be in the range of 3–5% (5).

Various salvage therapies are used for patients with hematologic malignancies who relapse after allo-HSCT including use of donor lymphocyte infusion (DLI), conventional chemotherapy, immunotherapy, CAR T cell therapy and in select patients second allo-HSCT is considered. The CPI administration as a salvage therapy after allo-HSCT can restore the T cell function, activate lymphocytes and induce strong GVT effect. On the other hand, it can also cause serious immune related adverse events including serious GVHD. Aggregated data from studies regarding CPI use after an allo-HSCT relapse disease showed that it is possible to achieve CR in 28% of relapse cases; PR noted in additional 19% of patients and stable disease in 7% of patients.

Depending on the nature of malignancy, other than its use in CML, the efficacy of DLI is limited with significant risk of GVHD. In comparison to low efficacy reported with historical DLI use, it may become possible to appropriately time the exposure and manipulate immune activation with a safe CPI dose in this difficult to treat population. Risk of GVHD with CPI exposure is around 23% if given to post-allo-HSCT population. About 14% of cases were reported with acute GVHD and 9% of patients suffered from chronic GVHD. It is debatable whether a particular dosage or proper timing of CPI exposure may be safer with good efficacy and low risk of GVHD. In a phase 1 clinical trial, when ipilimumab was administered to twenty-nine patients, in dose ranges up to 3 mg/kg (low dose), no GVHD was reported. Four patients developed immune adverse events such as polyarthropathy, hyperthyroidism, and grade IV pneumonitis. ORR was reported to be 17% with a median overall survival (mOS) of 24.7 months even in the low dose group (1).

In Davids *et al.* study, six patients received ipilimumab at a dose of 3 mg/kg and did not see any objective response with one patient developing chronic GVHD of the liver. Other patients (n=22) receiving a higher dose (10 mg/kg) showed ORR of 32% with a mOS of 28.2 months. Investigators reported chronic GVHD of the liver in two patients while one patient developed grade 2 acute GVHD of gut (2, 13). In 2017, Davids *et al.* administered ipilimumab to another cohort of fifteen patients at the dose of 5 mg/kg. ORR was reported to be 23% and GVHD developed in six patients (one acute and five chronic). These limited results indicate to investigators that they could administer ipilimumab safely up to a 3 mg/kg dose in post-allo-HSCT relapsed patients; however, at this dose the efficacy is low. Increasing the dose of the antibody increases the efficacy but also makes more patients prone to the risk of GVHD. The median time of drug administration after allo-HSCT was 12.2 months in Bashey *et al.* (1) and 22.5 months in *Davids et al.* (2). Lower incidence of GVHD at a lower dose (3 mg/kg) observed in Davids *et al.* and Bashey *et al.* could be due to the long interval between transplant and ipilimumab administration. In another study by Herbaux *et al.*, the patients who developed GVHD after CPI exposure were then administered nivolumab relatively early after allo-HSCT with the median time interval of 8.5 months. The patients who received nivolumab late after transplant with a median interval of 28.5 months did not experience GVHD (8). Most studies administered CPI at least three months after allo-HSCT and thus investigators can draw no conclusions regarding its safety and efficacy if used sooner than three months post-transplant. Available limited data suggests that investigators could minimize the risk of GVHD if they can increase the time interval between allo-HSCT and CPI exposure.

Prior history of GVHD appears to have a positive correlation with the increased risk of GVHD in patients treated with PD-1 blockers after they had disease relapse. In Herbaux *et al.,* nivolumab was administered to 20 patients at the dose of 3 mg/kg and it showed ORR of 95%. Six patients developed acute GVHD while none developed chronic GVHD (8). In another study by Haverkos *et al.*, 28 patients received nivolumab at the dose of 3 mg/kg and 3 patients received pembrolizumab at 200 mg/kg. Out of thirty-one, 17 patients developed GVHD (10 acute and 7 chronic cases of GVHD) (7). It is noteworthy that in both studies (Herbaux *et al.* and Haverkos *et al.)* a majority of patients who developed CPI related GVHD, had a prior history of GVHD (12 out of 17 cases in Haverkos *et al.* and all the 6 cases in Herbaux *et al.*).

Evaluation of the collective data shows that there is high incidence of hyper-acute, acute and chronic GVHD with prior CPI exposure in patients who later underwent allo-HSCT. The CPI use after allo-HSCT for post-transplant relapse has higher efficacy but the risk of GVHD is significant. Investigators found that higher drug doses, shorter intervals between CPI exposure and allo-HSCT and prior history of GVHD had a positive correlation with the response and the risk of GVHD. In addition, the CPI use causes long lasting immune activation, and risk of GVHD is elevated for many months. GVHD related mortality was higher in patients who received CPI before allo-HSCT. Owing to the limited data, we suggest that further clinical trials should assess the safety and efficacy of CPI in association with allo-HSCT. There are limitations of our study, which include heterogeneity of patient population, possibility of double counting of some patients, inconsistent non-standardized GVHD scoring reported on many available trials, possibility of incorrect categorization of

GVHD versus other immune mediated toxicities, lack of autopsy data to confirm exact cause of mortality and potential reporting biases.

Acknowledgments

Financial disclosure statement: This work was supported in part by grant P30 CA023074 from the National Cancer Institute, National Institutes of Health, Bethesda, MD. Authors declare that there is no conflict of interest with this manuscript. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Highlights

- The use of checkpoint inhibitors (CPI) in hematological malignancies before allogeneic hematopoietic stem cell transplantation (allo-HSCT) cause high incidence of hyper-acute (7%), acute (56%), and chronic (29%) graft versus host disease (GVHD).
- The use of checkpoint inhibitors in hematological malignancies after allo-HSCT show high efficacy but also increase the risk of GVHD (14% acute, 9% chronic).

Table 1:

Cases about checkpoint inhibitor use after allogenic stem cell transplantation.

Author Year	CPI	Dose (mg/kg)	Primary disease (n)	Response (n)	GVHD (grade)	Other Outcomes (n)
Onizuka*et al.* 2016	NV	0.5–2	HL (1)	PR (1)	GVHD worsened	NA
Angenendt*et al.* 2016	NV	3	HL (1)	CR (1)	none	NA
Villasboas*et al.* 2016	PZ	2	HL (2)	CR (1) PR (1)	none	NA
Chan *et al.* 2016	PZ	2	ALCL (1)	PR (1)	none	NA
Yared*et al.* 2016	NV	0.5–3	HL (1)	PR (1)	none	Pneumonitis, Hepatitis
Shad *et al.* 2016	NV	3	HL (1)	CR (1)	none	NA
Albring*et al.* 2017	NV[a]		AML (3)	CR (1) SD (1) PD (1)	GVHD (2) *	Myalgias
Singh *et al.* 2017	PZ	NA	HL (1)	CR (1)	GVHD (4)	Death = pneumonia
Kwong*et al.* 2017	PZ	2	NK/T cell Lymphoma (7)	CR (5) PR (1)	GVHD (2) *	NA
Godfrey *et al.* 2017	NV	3	HL (3)	PR (3)	none	Arthralgias, Conjunctivitis and Rash (2)
Cheikh*et al.* 2017	NV	3	HL (2)	CR (2)	GVHD (3) *	Death = fungal infection (1)
Boekstegers*et al.* 2017	PZ	3.3	ALL (1)	CR	GVHD (4)	Death
Covut*et al.* 2017	NV	NA	HL (2)	CR	none	Death = hepatic failure

* only one patient had GVHD

[a] 1 patient received single dose of 100 mg; 1 received a repetitive regimen of 0.3–1mg/kg weekly for 5 infusions;1 received two injections (100 mg each)

Abbreviations: AML= acute myeloid leukemia, ALL= acute lymphocytic lymphoma, ALCL= anaplastic large cell lymphoma, CPI= checkpoint inhibitor, CR= complete remission, GVHD= graft versus host disease, HL= classical Hodgkin's lymphoma, n= number of patients, NV= nivolumab, PD= progressed disease, PR= partial remission, PZ= pembrolizumab, SD= stable disease, NK: Natural killer, NA: Not available.

Table 2:

Safety and Efficacy of CPI therapy after allo-HSCT

Articlem Year	N	n	mFU (mo)	CPI	Doses (mg/kg)	Interval (Mo)	ORR (%)	Response (%)	aGVP (%)
Bashey *et al.* 2019	29	18[a]	12	IP	0.1–3[e]	12.5	17	CR (11) PR (6)	0
Schoch *et al.* 2016	9	NA	24	NV, IP, PZ	NA	14.4	NA	NA	11
David *et al.* 2016	6	6	15	IP	3	22.5	0	0	0
Herbaux *et al.* 2017	20	19	12	NV	3	23	95	CR (42) PR (53)	30[b]
David *et al.* 2017	22	22	15	IP	10	22.5	32	CR (27) PR (5)	5
David *et al.* 2017	15	13	9	IP	5	NA	23	PR (23)	7
David *et al.* 2017	8	6	8	NV	1;0.5[f]	NA	17	PR (17)	0
Haverkos *et al.* 2017	31	30	14	NV, PZ	3,200	26.4	77	CR (50) PR (27)	32[c, d]
Khouri *et al.* 2018	10	9	20.5	IP+LN*	3[g]	29;52[h]	44	CR (33) PR (11)	0

*Lenalidomide given in combination with Ipilumumab; GVHD after Lenalidomide administration

[a]evaluable patients for response receiving >1 mg/kg in the study

[b]25% had severe GVHD

[c]19% had severe (G3-G4) GVHD

[d]4 patients had overlap GVHD

[e]Dose escalation study; single infusion, starting with 0.1 mg/kg and increased to 0.33, 0.66, 1.0 and 3.0 mg/kg.

[f]Six patients received 1mg/kg, two patients received 0.5mg/kg

[g]Ipilimumab given for a total of 2 doses at 3mg/kg alternating with lenalidomide

[h]Patients with aggressive histology; patients with indolent histology.

Abbreviations: CPI: Checkpoint inhibitors, CR: Complete remission, Mo: Months, PR: Partial remission, allo-HSCT: allogeneic hematopoetic stem cell transplant, Interval: median interval between allo-HSCT and CPI administration, IP= Ipilimumab, mFU= median follow up, N= total number of patients, n= evaluable patients for response, NV= nivolumab, PZ= pembrolizumab, aGVHD: acute graft versus host disease, cGVHD: chronic graft versus host disease, ORR: Objective response rate, NA: not available.

Table 3:

Safety and Efficacy of CPI therapy prior to allo-HSCT

Article Year	N	mF U (mo)	CPI	Cycles	Interval> (d)	ORR (%)	Response (%)	aGVHD* (%)	Deaths (%) cGVHD (%)	
Schoch *et al.* 2016	11	8.0	NV/IP	4	43	NA	NA	36	00	0
Armand *et al.* 2016	17	8.7	NV	9	29	NA	NA	82	35	NA
Kasamon *et al.* 2017	17	4.6	NV	9**	28	NA	NA	65	35	NA
Merry men *et al.* 2017	39	12	NV/PZ	8	62	62	CR (36) PR (26)	44	10	41
Bekoz *et al.* 2017	11	2	NV	9**	30	73	CR(45) PR(27)	36	18	9
Cheikh *et al.* 2017	9	10	NV	8**	44	78	CR(78)	100	11	33
Covut *et al.* 2017	3	4.7	NV	11	NA	100	CR(100)	33	33	NA

*7% patients had hyper-acute GVHD and 20% patients had Grade 3–4 GVHD.

**Nivolumab was given at the dose of 3mg/kg; Dose not mentioned in rest of the studies.

Abbreviations: aGVHD= acute graft versus host disease,

allo-HSCT= allogeneic hematopoietic stem cell transplant, cGVHD: chronic graft versus host disease, CPI= checkpoint inhibitors, CR= complete remission, Cycles= median cycles, Interval= median interval between CPI administration & allo-HSCT, IP= ipilimumab, mFU= median follow up, mo= months, N= total number of patients, NV= nivolumab, ORR= objective response rate, PR= partial remission, PZ= pembrolizumab, NA: Not available, d: days.