ARTICLE

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Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial

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219 HIV-negative adults ≤70 years with primary CNS lymphoma (PCNSL) were enrolled in the randomized IELSG32 trial. Enrolled patients were randomly assigned to receive methotrexate-cytarabine (arm A), or methotrexate-cytarabine-rituximab (B), or methotrexate-cytarabine-thiotepa-rituximab (MATRix; arm C). A second randomization allocated patients with responsive/stable disease to whole-brain irradiation (WBRT) or carmustine-thiotepa-conditioned autologous transplantation (ASCT). First results, after a median follow-up of 30 months, showed that MATRix significantly improves outcome, with both WBRT and ASCT being similarly effective. However, sound assessment of overall survival (OS), efficacy of salvage therapy, late complications, secondary tumors, and cognitive impairment requires longer follow-up. Herein, we report the results of this trial at a median follow-up of 88 months. As main findings, MATRix was associated with excellent long-lasting outcome, with a 7-year OS of 21%, 37%, and 56% respectively for arms A, B, and C. Notably, patients treated with MATRix and consolidation had a 7-year OS of 70%. The superiority of arm B on arm A suggests a benefit from the addition of rituximab. Comparable efficacy of WBRT and ASCT was confirmed. Salvage therapy was ineffective; benefit was recorded only in patients with late relapse re-treated with methotrexate. Eight (4%) patients developed a second cancer. Importantly, MATRix and ASCT did not result in higher non-relapse mortality or second tumors incidence. Patients who received WBRT experienced impairment in attentiveness and executive functions, whereas patients undergoing ASCT experienced improvement in these functions as well as in memory and quality of life.

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INTRODUCTION

In recent decades, international cooperation has delivered substantial progress in the management of patients with primary CNS lymphoma (PCNSL), particularly for patients younger than 70 years. Several large randomized trials focused on important open questions have been completed or are ongoing. The IELSG32 study is the largest randomized trial comparing different induction chemo(immuno)therapy combinations and two different consolidation strategies in patients younger than 70 years with newly-diagnosed PCNSL [1, 2]. IELSG32 was conducted in 53 centers of five countries, covering an extensive geographical area, favoring generalizability of results, and providing a high level of evidence in this field. The primary study results, after a median follow-up of 30 months, demonstrated that the MATRix regimen (methotrexate, cytarabine, thiotepa, and rituximab) is significantly more effective than the other two induction arms, with higher rates of manageable hematological toxicity[1]. Moreover, this trial demonstrated that both whole-brain irradiation (WBRT) and high-dose chemotherapy supported by autologous stem cells transplantation (HDC/ASCT) are feasible and effective consolidation approaches; particularly after MATRix induction [1, 2]. However, in order to robustly assess the effects of these therapeutic approaches on overall survival (OS), late toxicity, incidence of secondary tumors, and cognitive impairment, longer follow-up is required. In a recent study from the Center for International Blood and Marrow Transplant Research registry on 603 PCNSL patients treated with different HDC/ASCT conditioning regimens, the 1-year non-relapse mortality was relatively high at 11%, in particular when thiotepa-busulfan-cyclophosphamide combination was used in patients older than 60 years [3], but more detailed reports in this setting are lacking. The incidence of secondary hematologic and solid tumors, a major concern in lymphoma patients treated with HDC/ASCT, remains to be defined in PCNSL. The latter is mostly due to the high mortality of PCNSL patients, the small number of transplanted patients (typically 20–30 patients per study), and the limited follow-up duration in prospective trials, with median values ranging between 15 and 45 months [4]. In the largest series of transplanted PCNSL patients in a prospective trial ($n = 73$), after a median follow-up of 57 months, no cases of secondary cancer were mentioned [5], but this remains to be confirmed after a suitably longer follow-up.

In line with other studies [6, 7], the IELSG32 trial demonstrated significant impairment of some cognitive functions in patients treated with WBRT, whereas patients treated with ASCT exhibited improvement in QoL and in most of the cognitive functions assessed [2]. Notably, a study based on longitudinal cognitive assessment for up to 5 years indicated that the improvement in cognitive functions recorded in the first 3 years post-treatment was followed by a decline at later time points and an increase in imaging abnormalities on MRI surveillance in both PCNSL patients treated with WBRT or HDC/ASCT [8]. This disturbing report underscores the need for long-term follow-up to better characterize delayed neurotoxicity in progression-free patients with PCNSL.

We therefore analyzed long-term data from the IELSG32 trial, with 90% of survivors being followed for more than 6 years. After a median follow-up of 88 months, we describe the association of treatment allocation (induction chemoimmunotherapy, WBRT, ASCT) with OS, incidence of second cancers, non-relapse mortality, neurocognitive function, and other late toxicities.

PATIENTS AND METHODS

Trial design and study group

This was a multicentre, open label, randomized phase II trial, with a two-step randomization (Fig. 1). Selection criteria were: (1) histologically proven diagnosis of high-grade B-cell non-Hodgkin lymphoma; (2) disease exclusively localized into the CNS, cranial nerves and/or eyes; (3) no previous treatment; (4) measurable disease; (5) age 18–70 years; (6) ECOG performance status score ≤3 (≤2 for patients aged 66–70). Patients with prior organ transplant or other forms of immunosuppression, with HBV, HCV and/or HIV infections were excluded. Patients with previous or concurrent malignancies were excluded, with the exception of surgically cured carcinoma in-situ of the cervix, carcinoma of the skin or other cancers without evidence of disease at least from 5 years; patients with a previous lymphoma were not eligible. Written informed consent was obtained from each patient once eligibility was confirmed. This trial conformed to the Declaration of Helsinki and was approved by the IRBs of the participating institutions.

At the first randomization, patients were allocated to receive one of three different chemo(immuno)therapy combinations as induction phase [1, 2]: methotrexate 3.5 g/m^2 (0.5 g/m^2 in 15 min, followed by 3 g/m^2 in 3-hour infusion) day 1; cytarabine 2 g/m^2 (1-hour infusion, twice a day, every 12 h) days 2 & 3 (arm A); or the same combination plus two doses of rituximab (375 mg/m^2, conventional infusion, days −5 & 0) (arm B); or the same methotrexate-cytarabine-rituximab combination plus thiotepa 30 mg/m^2, 30 min infusion, day 4 (arm C; MATRix regimen); each of the three arms repeated on a 21 day cycle. Patients with responsive or stable disease after induction, with adequate autologous peripheral blood stem cell (APBSC) collection were eligible for the second randomization, comparing WBRT (arm D; 36 ± 9-Gy tumor boost; photons of 4–10 MeV; five fractions/week; fraction size 180 cGy) and HDC/ASCT (arm E; carmustine 400 mg/m^2, day −6 and thiotepa 5 mg/kg, every 12 h, days −5 & −4). Patient with insufficient APBSC harvest were excluded from the second randomization, were treated with WBRT and considered evaluable for the first randomization endpoints. Diagnostic histopathological material of all registered cases was referred for central review. Registration, randomization, monitoring, local data entry, central data management, staging, autologous peripheral blood stem cell (APBSC) collection, follow-up as well as assessment of toxicity, cognitive decline and therapeutic response have been previously reported [1, 2].

The association of treatment with change in cognitive functions was assessed by a panel of neuropsychological tests currently used by the IPCG [9], and the Mini-mental Status Examination (MMSE) scale. Quality of life (QoL) was assessed by the EORTC-QLQ. These tests were performed at trial registration (baseline), after consolidation completion and every six months thereafter; the test batteries were administered by experienced neuropsychologists, and effects were analyzed on the per-protocol population; only patients who completed the planned treatment, did not experience lymphoma relapse, and had available information for baseline, post-treatment and at least two assessments during follow-up were assessable. Results of neuropsychological tests were centrally reviewed; data were analysed by the trial statistician and results of the statistical analyses were interpreted by the Chair neuropsychologists. Early read-outs of cognitive functions and QoL (differences between baseline and post-treatment scores) and data at two years of follow-up have been previously reported [2]. Late effects likely relate to the impact of treatment on cognitive functions, mostly expressed as cognitive decline or improvement after years of follow-up; these effects were analyzed estimating the delta value between scores of neuropsychological tests performed after treatment and at the last follow-up visit, per patient, grouped by consolidation arm, and comparing groups by t test.

Statistical considerations

The primary endpoints of the first and second randomizations were complete remission rate (CRR) after induction and 2-year progression-free survival (PFS), respectively. The A'Hern-Fleming single-stage phase II design was used. Toxicity (including acute, subacute and chronic forms and secondary tumors), OS, relapse rates, and neurotoxicity were the secondary endpoints. Survival curves were generated using the Kaplan–Meier method. PFS and OS were estimated according to Revised Response Criteria for Malignant Lymphoma [10]. Differences between therapeutic groups in PFS and OS were analyzed through the log-rank test. The statistical analysis was not done in a blinded manner. All the probability values were two-sided. All analyses were carried out using the Statistica 10.0 statistical package for Windows (Statsoft Inc, 2011, Tulsa, OK, USA). This study is registered as an International Standard Randomised Controlled Trial with ClinicalTrials.gov number NCT01011920.

RESULTS

Study population

Two hundred and twenty-seven patients were recruited at 53 Centers from five countries between February 19th 2010 and

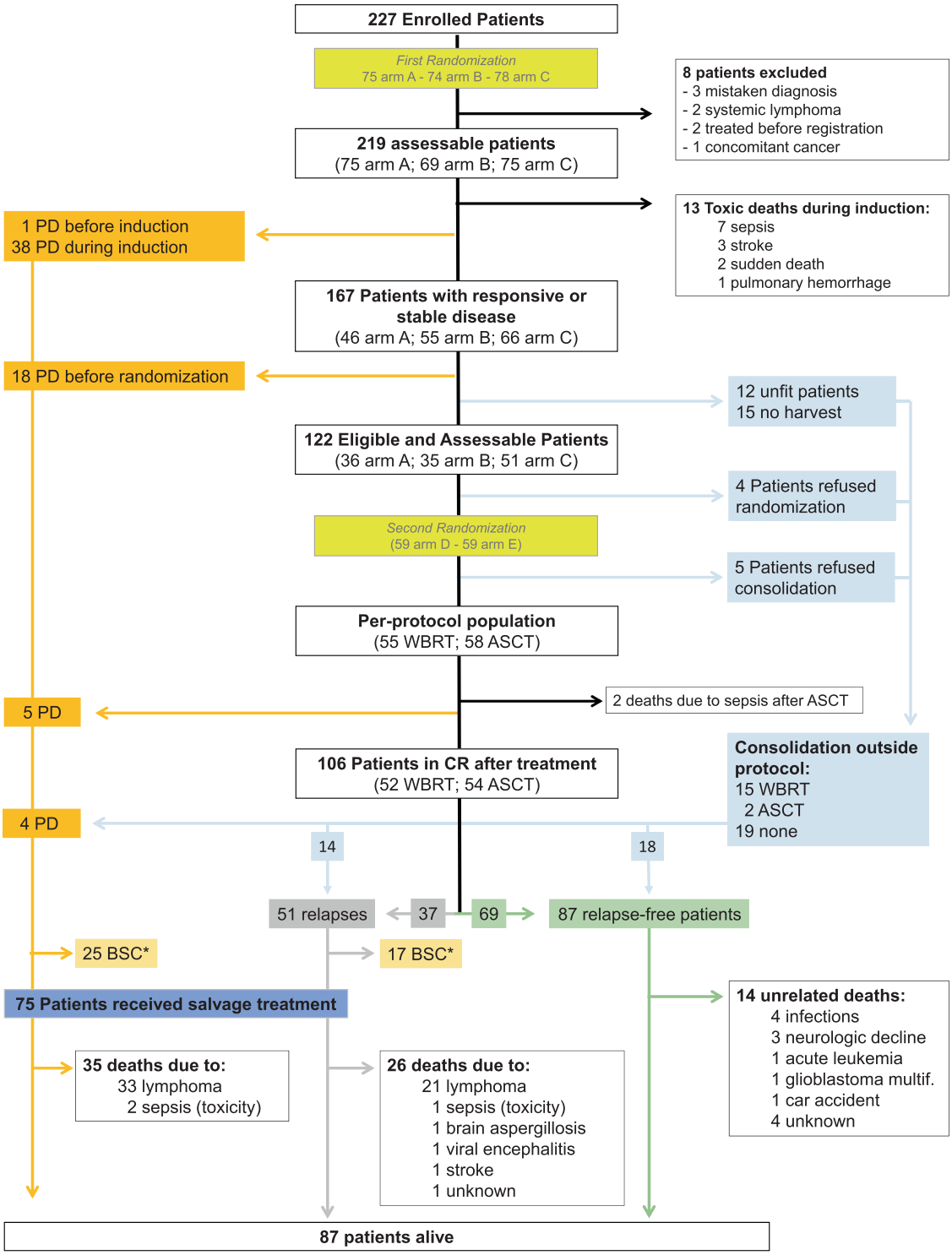

Fig. 1 Consort diagram. ASCT autologous stem cell transplantation, BSC best supportive care; PD progressive disease, WBRT whole-brain radiotherapy. *Forty-two patients did not receive salvage therapy and were managed with supportive care; all of them died of lymphoma within 4 months from relapse/progression.

August 27th 2014 (list of participating centers is provided in the Supplemental material). Study population, treatment tolerability and responses to induction and consolidation arms have been previously reported [1, 2]. In brief, arm C was significantly more active, with a CRR of 23% for arm A, 30% for arm B and 49% for arm C, with ORR (CR plus PR) of 53%, 74% and 87%, respectively. After induction, 122 patients (36 in arm A, 35 in arm B and 51 in arm C) were eligible for the second randomization; four patients refused the randomization, and, thus, 118 (97%) patients were referred to randomization. There were six protocol violations: four patients randomly allocated to arm D (WBRT) refused irradiation and were treated with ASCT and two patients randomly allocated to arm E (ASCT) were treated with WBRT according to physician's decision; five patients (two in arm D and three in arm E) refused

Table 1. Disease- and treatment-related events according to induction and consolidation arm (per-protocol bases).

	Total	Arm A ($n = 75$)	Arm B ($n = 69$)	Arm C ($n = 75$)	WBRT[a] ($n = 70$)	ASCT[a] ($n = 60$)	Others[b] ($n = 74$)
Toxic deaths (1st line)	15	7 (9%)	3 (4%)	3 (4%)	0 (0%)	2 (2%)	-
Progressive disease	66	26 (35%)	18 (26%)	13 (17%)	4 (4%)	2 (2%)	3 (4%)
Relapse after response	51	19 (25%)	17 (25%)	15 (20%)	22 (31%)	19 (32%)	10 (14%)
Salvage therapy	75	30 (40%)	22 (32%)	23 (31%)	15 (21%)	18 (30%)	42 (57%)
Second tumors[c]	8	1/38 (3%)	2/47 (4%)	5/59 (8%)	5/67 (7%)	3 (5%)	0 (0%)
Deaths during/after salvage[d]	7	4 (13%)	0 (0%)	3 (13%)	2 (13%)	2 (11%)	3 (4%)
Deaths of lymphoma	96	43 (57%)	32 (46%)	21 (28%)	19 (27%)	16 (27%)	61 (82%)
Deaths in relapse-free patients[e]	14	2/17 (12%)	6/28 (21%)	6/42 (14%)	9/44 (20%)	3/37 (8%)	2/6 (33%)

[a]Actually delivered consolidation regardless of random allocation.
[b]Denominator: all patients who did not receive WBRT or ASCT; patients died of toxicity during first line were excluded.
[c]Denominator: patients who completed the first-line treatment.
[d]Cause of deaths: bacterial septicemia (2), pneumonia, varicella-zoster virus encephalitis, stroke, brain aspergillosis, unknown.
[e]Cause of deaths: infections (4), cognitive decline (3), second tumor (2), car accident (1), unknown (4). Denominator: patients without lymphoma recurrence at the last visit.

consolidation. Therefore, per-protocol groups consisted of 55 patients treated with WBRT and 58 with ASCT. Both WBRT and ASCT were active and resulted in a remarkable increase in CR rate achieved after induction therapy, with a CRR of 95% after irradiation and 93% after transplantation.

Treatment- and disease-related events

Events occurring during the whole observation period of the trial are reported in Table 1. Fifteen (7%) patients died of toxicity during induction ($n = 13$) or after ASCT ($n = 2$). Sixty-six patients experienced PD: during induction in 57 patients, which was significantly less common in arm C, after WBRT in four and after ASCT in two. At a median follow-up of 88 (IQR 77–99) months, 51 patients with responsive disease experienced relapse. Relapse/PD occurred during the first year following trial registration in 84 (72%) patients, during the second or third year in 17 (15%) and later in 16 (14%). At progression or relapse, lymphoma involved the primary site of disease in 97% of cases (113/117); secondary sites of relapse (uninvolved at presentation) were eyes ($n = 2$), CSF ($n = 2$), eyes plus CSF ($n = 1$), testis ($n = 1$), and abdominal lymph nodes ($n = 1$). Forty-two (36%) of 117 patients with progressive/relapsed disease were considered unsuitable candidates for salvage therapy; all these patients died of lymphoma within four months from PD date. Seventy-five (64%) patients received second-line treatment: WBRT in 32 patients, high-dose-ifosfamide-based chemotherapy (R-IE, RICE or DeVIC regimens) in 16 and retreatment with HD-MTX-based combination (the same regimen used at randomization, or the same regimen ± other drug) in 19, with a complete remission rate of 39%, 38%, and 53%, respectively; moreover, three patients received a single-drug chemotherapy, three patients received carmustine-thiotepa-conditioned ASCT without induction chemotherapy, with long-lasting remission in two of them, and the two patients with systemic relapse were treated with R-CHOP. Seven (9%) of the 75 patients who received salvage therapy died due to causes different from lymphoma: bacterial infections ($n = 4$), varicella-zoster virus encephalitis, cerebral infarction, and sudden death. Overall, patients who experienced relapse after the first 3 years of follow-up had a significantly better survival after relapse than patients with refractory disease and patients who experienced relapse during the 2nd−3rd years of follow-up (2-year survival after relapse: 70 ± 11%, 11 ± 4% and 12 ± 8%; $p = 0.001$).

Secondary cancers were diagnosed in eight patients after 11–85 months of follow-up; all these cancers were diagnosed in patients who received a single line of anti-lymphoma treatment. Tumors were not related with induction or consolidation arms (Table 1). Four of the five tumors diagnosed in patients treated with WBRT arose outside irradiated tissues (two melanomas, Paget disease of the nipple, colon cancer); the exception was a case of glioblastoma diagnosed 70 months after WBRT. Three transplanted patients had secondary cancers (basal cell carcinoma, prostate carcinoma, acute erythroid leukemia). Patients with glioblastoma and acute leukemia did not receive anticancer therapy and died after a few weeks. The other six patients were referred for surgical resection and are relapse-free at 4, 16, 33, 36, 70, and 73 months, respectively.

For the whole study population, 87 (40%) patients are alive at a median follow-up of 88 (IQR 77–99) months; cause of death was lymphoma in 96 patients (Fig.1), infections (sepsis in 15, brain aspergillosis, pneumonia, varicella-zoster virus encephalitis) in 18, stroke in four, cognitive decline in three, second cancer in two, sudden death in two, pulmonary hemorrhage in one, and car accident in one; cause remains unknown in five patients.

Efficacy

Patients treated with MATRix combination (arm C) had a significantly better PFS and OS than patients treated in the other two arms (Fig. 2A, B), with a 7-year PFS and OS of 52% (95% CI = 47–57%) and 56% (95% CI = 52–60%), respectively for MATRix arm. Importantly, the favorable OS difference for arm B versus arm A achieved a statistically significant level after a median follow-up of 88 months. Notwithstanding longer follow-up, no differences in PFS and OS between consolidation arms were detected (Fig. 2C, D). Similar survival figures were obtained when analysis was performed on per-protocol population (data not shown).

Multivariable analysis showed that induction arm, number of lesions and IELSG risk score were independently associated with survival, whereas type of consolidation therapy did not influence outcome (Table 2).

Exploratory analyses

An analysis limited to the patients treated with MATRix regimen and consolidated by WBRT ($n = 31$) or ASCT ($n = 25$) showed a 7-year OS of 71% (95% CI = 69–73%) and 70% (95% CI = 67–72%) ($p = 0.74$), respectively (Fig. 2E, F).

Additional exploratory analyses focused on potential efficacy differences between consolidation strategies according to the response to induction and the potential impact of CSF/meningeal disease at diagnosis on the efficacy of consolidation therapies. These may be important parameters to drive the choice between WBRT and ASCT in routine practice. Accordingly, efficacy of consolidation arms was not related to response to induction, with a 7-year PFS of 54% (95% CI = 47–60%) after WBRT and 46% (95% CI = 34–57%) after ASCT ($p = 0.43$) for the 59 patients who achieved a partial response after induction, and 55% (95% CI = 48–61%) and 69% (95% CI = 67–71%) ($p = 0.21$) respectively, for

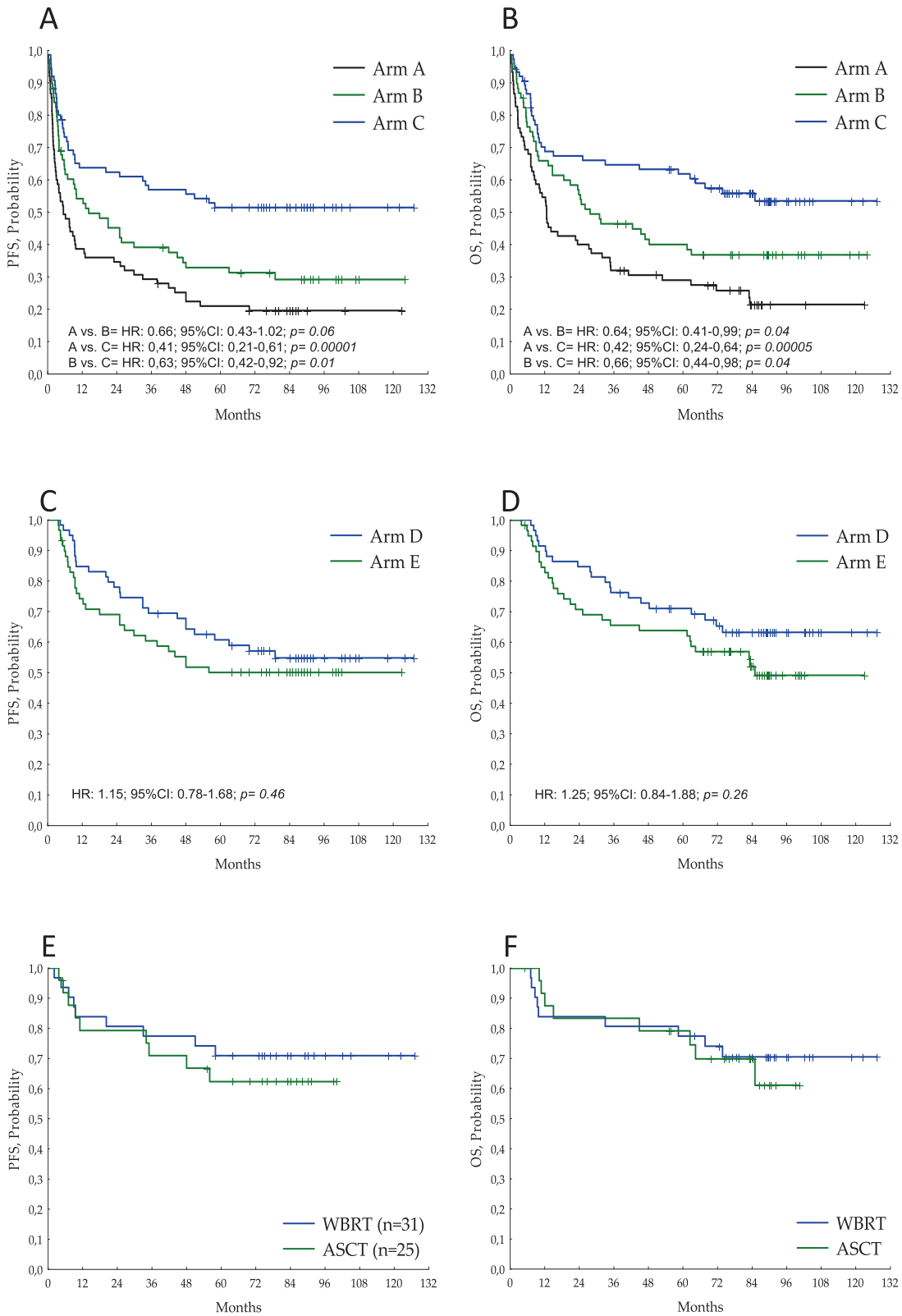

Fig. 2 Progression-free and overall survival curves. Progression-free (**A**) and overall (**B**) survival according to the induction arm and to the consolidation arm (**C**, **D**). The 7-year PFS was 20% (95% CI = 3–48%) for arm A, 29% (95% CI = 13–47%) for arm B and 52% (95% CI = 47–57%) for arm C, translating into a 7-year OS of 21% (95% CI = 4–47%), 37% (95% CI = 26–48%) and 56% (95% CI = 52–60%), respectively. Regarding consolidations arms: the 7-year PFS was 55% (95% CI = 50–60%) for arm D and 50% (95% CI = 43–56%) for arm (**E**) (HR: 1,15, 95% CI: 0,78–1,68; $p = 0.46$), and the 7-year OS was 63% (95% CI = 60–65%) and 57% (95% CI = 53–61%), respectively (HR: 1,25, 95% CI: 0,84–1,88; p = 0.26). Progression-free (**E**) and overall (**F**) survival of the 56 patients with disease responsive to MATRIX regimen who received consolidation whole-brain irradiation (WBRT) or autologous transplantation (ASCT).

Table 2. Multivariable analysis of overall survival.

Variables	Subgroups	Hazard ratio	95% lower CI	95% upper CI	p
IELSG risk	low vs. intermediate	0.93	0.58	1.51	*0.78*
	intermediate vs. high	1.88	1.20	2.94	*0.005*
Number of lesions	Single vs. multiple	1,45	1,00	2,11	*0,05*
Induction	Arm A vs. arm B	0.38	0.24	0.62	*0.0001*
	Arm B vs. arm C	0.36	0.21	0.62	*0.0002*
Consolidation	Arm D vs. arm E	1.16	0.77	1.75	*0.46*

the 65 patients who achieved a complete remission after induction therapy.

Positive CSF cytology may be a major limitation for the use WBRT in PCNSL patients. CSF cytology status was assessed in 162 patients, with positive results in 34 (21%); CSF involvement was not associated with survival outcomes, with a 7-year PFS of 32% (95% CI = 22–42%) for patients with negative CSF cytology, 38% (95% CI = 24–52%) for those with positive cytology and 35% (95% CI = 22–48%) for patients with unknown data. Among the three inductions arms, MATRix was associated with significantly better PFS in the subgroup of patients with CSF dissemination, with a 7-year PFS of 9% (95% CI = 0–10%), 30% (95% CI = 4–65%) and 69% (95% CI = 66–72%) ($p = 0.007$) respectively for arms A, B and C. Importantly, a trend to improved PFS in favor of ASCT (7-year: 67%; 95% CI = 62–71%) with respect to WBRT (7-year: 40%; 95% CI = 17–63%) in patients with CSF disease did not reach significant levels ($p = 0.32$).

Late effects of treatments on cognitive functions and QoL

Fifty-one (45%) of the 113 patients receiving consolidation (per protocol; 30 patients treated with WBRT and 21 treated with ASCT) were assessable for effects of consolidation strategies on cognitive functions and QoL. Distribution of clinical features in these two subgroups was similar to those of the whole study population, and there were no significant differences between arms. Full neuropsychological assessment was not conducted on the other randomized patients (29 patients after WBRT and 33 after ASCT) because: 35 patients experienced lymphoma relapse, seven died of toxicity or unrelated causes while relapse free, seven refused neuropsychological tests, and 13 had incomplete neuropsychological assessments (i.e., lacking of tests at baseline or at the end of treatment due to protocol violations). The latter was more commonly associated with necessity to start a timing treatment or with transient toxic effects after consolidation. Although these patients received neuropsychological tests at some other times of treatment and follow-up, transient disabilities preventing complete analysis cannot be excluded. The effect of treatment on cognitive functions and QoL was defined based on the differences between neuropsychological test scores and EORTC-QLQ assessed immediately after treatment and at the last visit of follow-up (Table 3). The median duration of the interval between these two assessments was 89 (range 38–127; IQR 79–102) months and 85 (range 55–123; IQR 77–91) months respectively for patients treated with WBRT and with ASCT. Significant impairment of some attentive/executive functions (WCST number of categories completed, WCST total error, WCST perseveration error) among patients treated with WBRT was recorded, contrasting with significant improvement in these attentive/executive functions, memory (Rey Auditory Verbal Learning Test – both Intermediate Recall and Delayed Recall) and QoL figures in patients treated with ASCT (Table 3). MMSE did not show a significant difference between consolidation arms.

DISCUSSION

To the best of our knowledge, the present analysis represents the longest follow-up among all the randomized trials performed in the field of PCNSL. These mature data from the IELSG32 study, at a median observation period of 88 months, allowed evaluation of the effect of randomly assigned treatments on OS, cognitive functions and incidence of late toxicity; particularly second tumors. Moreover, this analysis also provided insights into the role of conventional salvage therapy for relapsed/refractory PCNSL after intensive first-line treatment approaches in the modern era. Long-term results demonstrate that MATRix (arm C) was associated with a significantly superior OS compared to the whole study population, in each IELSG prognostic subgroup and among patients with other clinically important findings including CSF/meningeal dissemination and multiple lesions. Importantly, the relative efficacy of WBRT and ASCT did not alter over time, showing a 7-year OS close to 60% for both consolidation arms. The negative effect of WBRT on some cognitive functions and the positive effect of ASCT on both cognitive functions and QoL were confirmed with longer follow-up; these are important data that will inform the decision-making process for consolidation therapy in PCNSL. Secondary cancers were not more common among PCNSL patients treated with intensified strategies. In particular, the proportion of patients who developed secondary cancers after the combination of MATRix and ASCT was similar to those recorded for the other treatment arms. Taken together, these data underscore the safety and efficacy of MATRIX-ASCT in PCNSL patients ≤65 years old and in patients ≤70 with ECOG PS score ≤2.

The incidence of secondary hematologic and solid tumors in a recent SEER study on 40.714 patients with limited-stage DLBCL was 10%, without differences between nodal and extranodal forms and with a median interval between both diagnoses of 68 months [11]. In that study, PCNSL were excluded. In a recent update of a randomized trial addressing ASCT as part of first-line treatment in 275 patients with aggressive B-cell lymphoma, the risk of secondary cancers was 8% after a median follow-up of 9.3 years, with no difference between conventional-dose and myeloablative first-line treatments [12]. Acute myeloid leukemia and myelodysplastic syndrome are the most common hematological malignancies seen in this context, with a median time to secondary tumor diagnosis of 44 months. Solid tumors are typically carcinomas arising in a wide number of organs, and are diagnosed later, with a median of 72 months [12]. The incidence of secondary cancers in patients with PCNSL was not established before the IELSG32 trial, mostly due to the high mortality of PCNSL patients, the small number of patients treated with ASCT and the limited follow-up duration in reported series [4]. The findings of the IELSG32 trial suggest that incidence of second cancers in PCNSL patients younger than 71 years treated with modern approaches is 3.6%, with similar rates between irradiated and transplanted patients. There was a single case of secondary hematological tumor (acute erythroid leukemia after ASCT) and a single tumor arising within the irradiated volume (high-grade glioma after WBRT); these were the only two cases of death due to secondary cancers. The other six patients with secondary tumors achieved a durable remission after surgical resection; four of which were cutaneous tumors. These findings suggest that intensified, modern treatment for PCNSL is not associated with an increased risk of second cancers, and that most of the few

Table 3. Changes in cognitive functions assessed at the last visit (median follow-up: 88 months).

Test	WBRT arm ($n = 30$)	ASCT arm ($n = 21$)	p value[#]
Digit Forward	0,65 ± 3,73	−0,21 ± 1,51	0.20
Digit Backward	0,53 ± 3,06	0,89 ± 1,72	0.46
Trail Making Test A[a]	4,27 ± 6,50	4,17 ± 4,79	0.75
Trail Making Test B[a]	23,88 ± 8,40	24,80 ± 6,53	1.00
Trail Making Test B-A[a]	15,88 ± 7,38	9,00 ± 5,71	0.77
Brief Test of Attention	3,08 ± 5,37	0,50 ± 1,24	0.23
WCST Categories Completed	−0,07 ± 1,90	2,63 ± 0,90	0.002
WCST Number of Total Error[a]	−3,60 ± (−6,6)	8,88 ± 3,56	0.006
WCST Perseveration Error[a]	−0,70 ± (−6,3)	10,00 ± 2,60	0.001
Rey Auditory Test—Delayed Recall	0,50 ± 0,67	−0,11 ± 2,61	0.43
Rey Auditory Test—Total Learning	0,23 ± 0,99	1,87 ± 0,89	0.36
Rey Complex Figure Copy	−0,75 ± 3,48	0,81 ± 3,62	0.05
Rex Complex Figure—Delayed Recall	−1,00 ± 4,00	9,50 ± 4,09	0.001
Token Test	0,57 ± 5,39	0,33 ± 4,77	0.56
Phonetic Verbal Fluency	1,68 ± 16,0	−0,22 ± 4,14	0.81
Semantic Verbal Fluency	0,68 ± 8,91	3,77 ± 4,91	0.69
Grooved Pegboard Test—Left Hand[a]	9,83 ± 1,54	9,84 ± (−1,9)	0.65
Grooved Pegboard Test—Right Hand[a]	12,36 ± 4,47	7,53 ± (−2,5)	0.32
EORTC QLQ	0,38 ± 2,40	2,78 ± 2,08	0.001
Mini-Mental State Examination	0,80 ± 3,22	0,60 ± 2,35	0.87

Results are reported as mean values ± SD of the differences between scores of tests done immediately after treatment and at the last visit of follow-up. Positive values indicate function improvement.

[a]Differences can be positive or negative, but signs of these tests were changed (from negative to positive and vice versa) to improve interpretation.

[#]p values indicate whether there were significant differences between patients treated with WBRT or ASCT (per protocol).

WBRT whole-brain radiotherapy; *ASCT* autologous stem-cell transplantation, *WCST* Wisconsin Card Sorting Test, *EORTC QLQ* European Organisation for Research and Treatment of Cancer quality-of-life questionnaire.

recorded cases are diagnosed in limited stage and can be successfully managed.

With the major limitation that enrolled patients were assessed at different times of follow-up (last visit), and with other previously recognized methodological limitations [2], results of the IPCG neuropsychological panel and EORTC QLQ at a median follow-up of 88 months confirm the significant decline in some attentive/executive functions in irradiated patients, and a significant improvement in these functions, memory and QoL in transplanted patients. These findings are in line with results of the PRECIS trial and other studies performed in PCNSL patients, and suggest that radiation dose is proportionately associated with risk of neurotoxicity [7, 13, 14]. As previously reported [2], severity of cognitive decline after WBRT seems to be lower in the IELSG32 trial, than in previously reported series, which may be explained in part by the use of lower radiation doses in the IELSG32 trial in comparison with prior studies [13, 14]. Conversely, neurotoxicity rates of IELSG32 and PRECIS [7] trials should be compared with caution considering some relevant differences in trial designs. In particular, upper age limit was very different (60 years for PRECIS and 70 years for IELSG32), with a higher proportion of patients older than 60 years, that is at increased neurotoxicity risk, in the IELSG32 trial (39% vs. 0%). The difference in induction regimens may also be another confounding factor. Despite a lower CRR after induction (43% for PRECIS and 54% for IELSG32), a higher proportion of PRECIS patients received consolidation (69% vs. 54%), whereas, unexpectedly, a greater percentage of PRECIS patients had residual disease after consolidation (42% vs. 6%). Equally important, neuropsychological assessments were different: the PRECIS protocol did not include the IPCG neuropsychological panel, and cognitive functions were assessed before consolidation and not after consolidation like in the IELSG32 trial. Thus, any difference in terms of cognitive decline between IELSG32 and PRECIS trials may not be explained only by the 4-Gy difference in WBRT dose (40 Gy for PRECIS and 36 Gy for IELSG32), but by several other discrepancies between trial designs.

The definition of disease-related and treatment-related factors associated with an increased neurotoxicity, like number and size of lesions, induction regimen, and use of radiation boost, among others, remains a focus for future studies. This was not explored in this trial for methodological reasons as the analysis of effects on neurocognitive functions included 20 different tests; all of which were continuous variables without censoring data by definition. This rendered the assessment of treatment variables by multivariable tests impracticable and at high risk of unreliable conclusions. Another important open question regards the impact of iatrogenic cognitive decline on everyday life, which has never been investigated in detail in PCNSL survivors. In the IELSG32 trial, we can hypothesize that severe neurocognitive dysfunctions were uncommon in the 61 long-term survivors who received consolidation and did not experience lymphoma relapse as only four (6%) of them (two in arm D and two in arm E) had an ECOG PS > 1 at the last visit. However, PS is a rather crude finding that can be affected by multifaceted factors. Accordingly, suitable methodologies evaluating the impact of iatrogenic cognitive decline on activities of daily living according to educational and socioeconomic status (i.e., Environmental Status Scale or Work Ability Index) should be included in future PCNSL trials, and the effects of age and pre-existing vascular or neurological comorbidity should be better investigated.

A recent retrospective study showed that, when used in everyday practice, MATRix is associated with comparable efficacy and tolerability as reported in the IELSG32 trial [15]. In fact, MATRix was associated with a 79% ORR, 36% CRR, a 63% 2-year PFS, and a

6% TRM in an international series of 156 consecutive patients with newly diagnosed PCNSL treated at 13 centers from UK, Italy and Germany. These results are particularly impressive considering that one-third of treated patients were older than 70 years, had ECOG-PS ≥ 3 or significant comorbidity, which could be associated with higher risk of toxicity and lower efficacy. Notwithstanding these encouragingly similar results from both clinical trials and routine practice, it is important to recognise the impact of neurocognitive dysfunction and impaired PS of many patients at initiation of therapy. This remains a major challenge associated with severe toxicities after the first course of MATRix. Strategies to improve patients' condition before starting MATRix should be addressed in future trials. Likewise, strategies to improve efficacy and tolerability of consolidation WBRT and ASCT should be explored. According to the preliminary data of the RTOG1114 trial [16], low-dose WBRT deserves further investigation, perhaps in comparison with ASCT. De-escalation of ASCT, using a non-myeloablative chemotherapy, has been hypothesized as a suitable strategy to improve feasibility and to extend indication to older patients. This strategy is being investigated by two randomized trials under the sponsorship of the ALLIANCE and IELSG, respectively. Preliminary results of the ALLIANCE 51101 trial suggest that consolidation with non-myeloablative doses of etoposide and cytarabine are associated with poorer PFS than carmustine-thiotepa-conditioned ASCT [17], whereas confirmatory data from the IELSG43/MATRix trial, which compares non-myeloablative chemotherapy with DeVIC regimen with the same carmustine-thiotepa-conditioned ASCT [18], are pending. Long-term results of these studies will define the value of ASCT de-escalation as part of upfront treatment of PCNSL.

These updated results of the IELSG32 trial add new insights on the role of rituximab as part of first-line treatment for PCNSL patients. The comparison between arm A and arm B performed after a longer follow-up showed a significant improvement in OS with the addition of rituximab, which contrasts with results from the randomised phase III HOVON 105/ALLG NHL 24 trial [19]. This discrepancy may be explained, at least in part, by different treatment intensity in the two trials. Induction in the HOVON 105/ALLG NHL 24 trial consisted of two courses of MBVP chemotherapy, with or without six doses of rituximab, followed by one course of HD-AraC. Patients aged <60 years underwent consolidation WBRT at a reduced dose (20 Gy), whereas patients older than 60 years did not receive any consolidation. The addition of rituximab has been uninfluential on event-free survival (primary endpoint), whereas PFS was numerically improved but not statistically significant. It is possible that short-term chemotherapy, low-dose irradiation and, specially, the lack of consolidation in elderly patients could have hampered any benefit from the addition of rituximab. This interpretation is supported by an unplanned subgroup analysis showing that patients <60 years had a significant benefit from rituximab, whereas older patients >60 years, treated without consolidation, tended to show the opposite effect. A recent meta-analysis of study-level data from the two randomised trials (i.e., IELSG32 and HOVON 105/ALLG NHL 24 trials) has confirmed a PFS benefit with the addition of rituximab, though with low certainty [20].

The limited efficacy of salvage therapy in the IELSG32 trial is in line with previous retrospective studies. In large "real-life" studies, 25% of patients are primary refractory to HD-MTX-based chemotherapy, and other 25% of patients experience relapse after initial response [21]. Most relapses are associated with neurocognitive dysfunction and very poor prognosis [22]. Despite enrollment in a prospective trial, one-third of IELSG32 patients with refractory or relapsing disease were considered unsuitable candidates for salvage therapy and received only palliative care. In a prior retrospective study on 27 PCNSL patients, salvage WBRT has been associated with a 74% ORR and a median survival of 11 months [23]. In the IELSG32 trial, WBRT was indicated at first relapse in 32 patients, resulting in a 42% ORR and a median survival after relapse of 8 months, with only three patients alive at 2 years. These poorer results are related to the use of WBRT mostly in patients with chemorefractory disease, which exhibited a very poor prognosis, with a 2-year survival after relapse of 11 ± 4%. Regardless of the adopted salvage therapy, patients who experienced a relapse during the second or third year of follow-up had a similar survival after relapse (2-year: 12 ± 8%) than patients with refractory disease, whereas patients who experienced relapse after the third year of follow-up exhibited the best outcome, with a 2-year survival after relapse of 70 ± 11%. The latter subgroup of patients were often re-treated with HD-MTX-based polychemotherapy, achieving a durable response in two thirds of cases, which, in line with a previous retrospective study [24], suggests that HD-MTX rechallenge is an effective salvage treatment in patients who experience a durable remission after first-line HD-MTX-based combination therapy.

In conclusion, the present analysis of the IELSG32 trial was performed after the longest follow-up period among all published randomized trials in the field of PCNSL. These data demonstrate that MATRix regimen is associated with excellent long-term outcomes and that WBRT and ASCT had comparable efficacy. Patients treated with MATRix and consolidation had a 7-year OS of 70%, without a difference between WBRT and ASCT. IELSG score, number of lesions and induction arm were independent predictors of OS. MATRix and ASCT did not result in a higher incidence of non-relapse mortality or second tumors by comparison with the other IELSG32 arms, whereas WBRT led to impairment of specific cognitive functions.

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AUTHOR CONTRIBUTIONS

AJMF, KC, EP, JF, FC, EZ, and GI were responsible for designing the review protocol, writing the protocol and report, analysing data, interpreting results, and writing the manuscript. CC and MF was responsible for revision and analysis of neuropsychological tests and results interpretation. AN performed statistical analysis. CPF, ES, PLR, MB, AF, FI, MK, AR, CH, PWJ, KML, TP, JSG, MB, GH, UK, SS, JP, AT, LO, FP, MZ, SWK, HJS, BH, MR, JS, LT, GC, and EP registered and treated patients, and provided clinical data. MP and MD performed central pathology review. LSP performed central radiology review. AF, KeC, EB, and NI acted as data managers and study coordinators, contributed to data extraction and provided feedback on the report. All the authors approved manuscript and submission.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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